

THESIS

ON

THE PATHOLOGY AND PATHENOGENESIS OF PORTAL HYPERTENSION

SUBMITTED FOR THE DEGREE OF

M.D.

By

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PREFACE

Since the publication in 1947 of Professor Himsworth's monograph on "Disorders of the Liver" and the work on which it was based, renewed interest has been taken in the pathology of cirrhosis of the liver for the views put forward in these articles, while they do not completely explain the sequence of events leading to the development of human cirrhosis, provide a fresh basis on which to build further theories. It has been recognised for many years now that the changes in the liver are accompanied - some said preceded - by pathological changes in the portal venous system and in the spleen. Along with these changes there is congestion of the portal system of veins and the development between it and the systemic veins of anastomotic channels. Rupture and uncontrollable bleeding from the collateral channels is a frequent cause of death in these cases (Preble, 1900) and recently surgeons have turned their attention to the problems which the presence of these varicosities present.

Similar oesophageal varicosities are found in the absence of cirrhosis of the liver where there is a block in the portal or splenic veins. These again are produced by long-continued congestion and gradual increase in pressure in the portal venous system, i.e., portal hypertension. This portal hypertension, as well as leading to the production of oesophageal varices, gives rise to splenomegaly and to changes in the portal and splenic veins. Portal hypertension, therefore, can be caused by cirrhosis of the liver or blockage of the portal or splenic veins and study of its pathology necessitates careful examination /

examination of the liver, portal and splenic veins and the spleen in each case. When this is done in the light of the recent developments and experimental work in the etiology of human cirrhosis and an understanding of the blood supply of the liver has been obtained, it is possible to consider the various theories which have been put forward to account for the development of portal hypertension.

To help further in an understanding of the reasons why portal hypertension should occur in cases of cirrhosis of the liver, the vascular trees of several normal and cirrhotic livers were injected.

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PART I

THE LIVER

Cirrhosis of the Liver

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INTRODUCTION

During the past decade considerable advances have been made in our knowledge of the processes involved in the production of the condition we know as cirrhosis of the liver. These advances are admirably reviewed and set out by Professor H.P. Himsworth in his monograph "Lectures on the Liver and its Disorders" (1947). Up till about ten years ago all attempts to produce experimentally a cirrhosis comparable to that seen in man had failed, though many systemic investigations of possible toxins and poisons had been carried out, investigations summarised at some length by Mallory (1932) and Moon (1934).

When the importance of Best's work (1932) on the part played by choline in fat metabolism in the liver was realised, a new field was opened and the importance of dietary deficiencies in the production of cirrhosis in small mammals has been neatly and apparently conclusively proved by Himsworth and Glynn (1944) and Glynn and Himsworth (1944). According to these authors, adequate quantities of choline and cystine must be present, and available, in the diet, for the proper functioning of the liver cells. Deficiency of either of these substances gives rise to two separate and quite different processes, both leading terminally to the occurrence of a "cirrhotic" liver.

When choline, which acts as a lipotropic substance, is present in the diet in inadequate amounts, fatty changes occur in the liver with eventual atrophy of liver cells, proliferation of /

of fibrous tissue from the portal tracts and around the central veins, and distortion of the liver lobule. The features of this process are its gradual onset and its diffuse nature, the whole liver and every lobule being affected. This process is a diffuse hepatic fibrosis.

On the other hand, when a deficiency of cystine is present no histological changes are noted for a period of a few weeks and then there is sudden death of liver cells. The process, acute massive necrosis, probably mainly for reasons of local vascular supply, is essentially a patchy one, the hepatic cells of small groups of lobules becoming necrotic while neighbouring small groups of lobules show little change. Scattered through the liver there are therefore small areas of necrosis and haemorrhage alternating with more normal areas, in marked contrast to the lesions in diffuse hepatic fibrosis where there is no death of cells and no completely normal areas remain. Subsequently there is collapse of the small areas of damaged liver with the formation of broad bands of fibrous tissue and hyperplasia of the cells in the remaining less affected areas. With the collapse and hyperplasia, distortion of the liver in this type of cirrhosis - post-necrotic scarring - is a prominent feature of the "healed" state.

Even in 1911 Mallory had recognised post-necrotic scarring calling it "toxic cirrhosis" and that normal lobules, and broad bands of fibrous tissue may occur in cirrhotic livers was recognised by Epplen (1922). Though these authors realised that the picture in these cases was the result of an episode of acute liver damage, little more was known about it.

It /

It has already been noted that Himsworth and Glynn's observations were made on small mammals, and there is still considerable doubt as to their exact significance when considered in relation to the production of cirrhosis in man. Several observations have however been made which suggest that the etiology of human cirrhosis is connected with the ideas which are discussed above.

The Gillmans (1944) in East Africa, and Waterlow (1948) in the West Indies, have published the results of investigations into the influence of diet on the incidence of fatty infiltration and cirrhosis of the liver in under-nourished native populations. They advance the theory that dietary deficiency is a cause of cirrhosis in man. Professor Himsworth (1947) suggests that alcohol acts as a cirrhotic agent in man only by virtue of the fact that its inclusion in the diet diverts money from the purchase of proteins and also involves the combustion of carbohydrate in place of protein.

It would appear therefore that Professor Himsworth's experimental results probably do have some application to human pathology, so when this study was undertaken it was decided to examine as many cirrhotic livers* as possible, with a view to trying to decide whether the basis of the liver lesion was a diffuse hepatic fibrosis or a post-necrotic scarring, and whether such a distinction could be made in these cases. It was /

* A liver was taken to be cirrhotic when any one of the following lesions was present:

- (1) It was obviously nodular.
- (2) There was an excess of fibrous tissue.
- (3) There was marked distortion of the lobular architecture.

was also hoped that if any case did not readily fit into one or other group, some explanation for this might be found.

The case notes and the livers of the cases available for study were carefully examined and are described with this end in view, the following criteria being taken as indicative of the type of lesion present:

(1) Marked fatty changes associated with a fine fibrosis and distortion of the lobular pattern - the picture of choline deficiency - indicated the presence of a diffuse hepatic fibrosis.

(2) The presence of even one normal liver lobule in a section otherwise showing cirrhotic lesions indicated that the case was one of post-necrotic scarring.

(3) If on naked eye examination of the liver there were large nodules, i.e. nodules greater than 1 cm. in diameter, or marked distortion of the organ by broad bands of fibrous tissue, these findings were taken to indicate the presence of post-necrotic scarring.

For the purpose of this investigation it was considered that the criteria selected on which to base a diagnosis of the type of cirrhosis of the liver present should be as strict as possible. The presence of any one of the factors enumerated above would, on the basis of Professor Himsworth's theories, be a very definite indication as to the type of cirrhosis with which we are dealing in that particular case. Following his theories further, it would be logical to suggest that a shrunken, diffusely nodular liver in which the nodules were less than 1 cm. in /

in diameter would indicate the presence of a diffuse hepatic fibrosis, but, for reasons which will emerge later in the chapter, this factor will not at present be taken into consideration.

After the description of the material, the next step is to describe the findings in the liver tissue in as much detail as possible. The description should be made in which an attempt is made to determine the group to which each case belongs, and any points of interest arising out of the case are noted.

Following the descriptions of the cases some points of interest emerging from their study will be taken up and the findings as a whole discussed.

Where possible, more than one section was prepared from the liver in each case, and when two sections were obtained one was usually from the right lobe and one from the left.

Case No. 1

187/46. Male, age 47. Occupation: not known.

History:

Shortly before death the patient had a bilateral emphysema performed. This was followed by an acute illness with signs of a right hemiplegia. At post mortem examination a meningioma was discovered and also acute bronchiectasis superimposed on an older lesion.

Liver (1320 g.):

The surface was smooth but slightly irregular, and on section, though a lobular architecture was not seen, no obvious abnormality was noted.

Microscopically (1 section): The portal tracts showed a slight tendency to clumping and stood out clearly because of the presence around them of a slight increase in fibrous tissue and one or two small proliferated bile ducts. The liver cells showed a few double nuclei and occasional slight

THE CASE MATERIAL

Attached to the detailed description of the naked-eye and microscopical findings in the liver there is in each case a short history giving the immediate cause of death if this was not directly connected with the condition of the liver. After the descriptions a short comment is added in which an attempt is made to determine the group to which each case belongs, and any points of interest arising out of the case are noted.

Following the descriptions of the cases some points of interest emerging from their study will be taken up and the findings as a whole discussed.

Where possible, more than one section was examined from the liver in each case, and when two sections were examined one was usually from the right lobe and one from the left.

Case No. 1

487/46. Male, aet. 43. Occupation: not known.

History:

Shortly before death the patient had a bilateral antrostomy performed. This was followed by an acute illness with signs of a right hemiplegia. At post mortem examination a meningioma was discovered and also acute bronchiectasis superimposed on an older lesion.

Liver (1320 g.):

The surface was smooth but slightly irregular, and on section, though a lobular architecture was not seen, no obvious abnormality was noted.

Microscopically (1 section): The portal tracts showed a slight tendency to clumping and stood out clearly because of the presence around them of a slight increase in fibrous tissue and one or two small proliferated bile ducts. The liver cells showed a few double nuclei and occasional slight /

slight variation in nuclear size. There was in no place any normal lobular arrangement though occasionally around portal tracts or a recognisable central vein a radial arrangement of cords of liver cells could be made out. Both the portal veins and central veins were distended and packed with red blood corpuscles.

Comment:

This case is of interest mainly because of the absence of fibrosis in an otherwise cirrhotic liver. Death appeared to be due to factors other than the condition of the liver.

Case No. 2

33/48. Male, aet. 49. Occupation: miner, surface worker.

History:

The patient was known to have an enlarged spleen for 3 years before his death. He died of portal vein thrombosis and mesenteric infarction. He lived alone so that there is a possible dietary basis for his hepatic condition.

Liver (1280 g.), (Fig. 5):

Showed a moderate diminution in size without any definite distortion of its shape. The surface was pale, coarsely and fairly evenly nodular, the nodules being mainly about 0.7 cm. in diameter. On section this nodularity was seen to extend diffusely through the liver without any obvious increase in fibrous tissue. The whole organ was pale brown in colour.

Microscopically (3 sections): There were similar changes in all sections. The absence of excess fibrous tissue through the liver was confirmed, only a few portal tracts immediately below the surface showing very slight increase in fibrous tissue around them, with slight proliferation of bile ducts and a few lymphocytes present. The remainder of the parenchyma was composed of completely irregularly arranged liver cells with no evidence of normal lobular arrangement. These cells showed only slight nuclear irregularity and a few double nuclei to be present. The portal tracts were scattered and few in number, with one or two showing occasional small proliferated bile ducts. Central veins were only occasionally identified and around a few of them there was slight collagenous thickening.

Comment: /

Comment:

The main feature in this case is the lack of fibrosis in the liver. Apart from the facts that splenomegaly had been present for 3 years before death and that he lived alone, there were no further points of interest.

Case No. 3

74/48. Female, aet. 66. Occupation: housewife.

History:

There had been loss of weight for 6 months, diarrhoea and vomiting for 3 weeks with more recent vomiting and abdominal distension. The patient was delirious on admission and lapsed into coma.

Liver (780 g.):

Was grossly shrunken and regularly nodular with no marked distortion of any one lobe.

Microscopically (1 section): There was gross irregularity of the liver pattern, the parenchyma being divided into small nodules with no element of normal architecture visible. The nodules of liver tissue were small and varied greatly in size. The hepatic cells showed diffuse and quite well-marked fatty changes with little evidence of nuclear activity. No central veins were recognised. The fibrous tissue was active-looking and contained many small proliferated bile ducts and lymphocytes. It encircled the small nodules of liver cells and extended also into a few of the nodules.

Comment:

The histological appearance of thin active-looking strands of fibrous tissue in association with small nodules of liver cells showing considerable fatty changes, suggest that this case is one of diffuse hepatic fibrosis, a diagnosis further substantiated by the naked-eye appearance of the liver. Death in this case was probably mainly due to the condition of the liver.

Case /

Case No. 4

153/48. Female, aet. 34. Occupation: not known.

History:

There was a history of "fluctuating jaundice" for 9 months before death. Death was due to gradual liver failure.

Liver (1200 g.):

Was soft and mottled with small areas of haemorrhage scattered over its surface and throughout the parenchyma.

Microscopically (2 sections): Post mortem changes were well advanced for few recognisable liver cells were present and any R.B.Cs. present were lysed. The parenchyma was composed of large masses of necrotic cells around small groups of which ran faintly staining bands of collagen. Here and there were small areas of haemorrhage. Portal tracts appeared to be diminished in number and they showed an increase in the amount of fibrous tissue around them and a few extra small bile ducts. Recognisable central veins too were few in number and no normal lobular architecture could be identified.

Comment:

In view of the similarity both in the clinical history and in the pathological appearance between this case and Case No. 29 which originated as an infective hepatitis, this case may also be regarded as one of an "acute cirrhosis" following on an attack of infective hepatitis. (See also - DISCUSSION - Page 50 - Infective Hepatitis).

Case No. 5

167/48. Male, aet. 57. Occupation: not known.

History:

Two and a half years and 6 months before admission the patient had had successive coronary thromboses, and during the 3 months prior to death he had been suffering from gradually increasing cardiac failure.

Liver (1620 g.):

Was coarsely nodular with no marked distortion. It was described as a typical portal cirrhosis.

Microscopically /

Microscopically (1 section): No normal liver architecture was visible, the parenchyma being composed of cords of liver cells showing no definite arrangement but forming small ill-defined nodules. There was little excess of fibrous tissue though it was slightly increased in amount around the portal tracts with one or two small reduplicated bile channels. Only in one or two places did thin strands of fibrous tissue run out into the surrounding tissue. The hepatic cells in small areas showed moderately well-marked fatty changes and in general slight nuclear irregularity with a few double nuclei. Throughout the section there were numerous small areas where the liver cells showed pallor of their cytoplasm, and there was a slight increase in collagen with occasional small haemorrhages. These areas are probably due to ischaemic changes.

Comment:

There is no clue as to the possible pathogenesis of the cirrhosis in this case, and the main points to note are the history of possible long-standing congestion and the presence of ischaemic changes in the liver.

Case No. 6

197/48. Male, aet. 75. Occupation: retired.

History:

Following an operation for acute appendicitis, an intraperitoneal haemorrhage occurred. The patient also suffered from silicosis and pulmonary tuberculosis.

Liver (1890 g.):

Was noted as showing a suggestion of slight nodularity but no obvious naked-eye cirrhosis.

Microscopically (1 section): There was gross distortion of the normal lobular architecture, no normal areas being visible. The liver cells were arranged in irregular cords and showed considerable irregularity of nuclear size and a few double nuclei. Post mortem changes were marked in part of the section, with collagenous changes around and between individual liver cells in some areas. There was no "lobularity" and only a very slight excess of fibrous tissue around the portal tracts. The portal tracts were few in number and they showed a minimal lymphocytic infiltration and bile duct proliferation. Scattered throughout the section there were /

were one or two small areas of congestion and cellular infiltration - possibly anoxic in origin.

Comment:

There is no indication from what type of cirrhosis this case originated.

Case No. 7

209/48. Male, aet. 34. Occupation: barman.

History:

The patient was known to be a heavy drinker. He was admitted to hospital with broncho-pneumonia after a drinking bout.

Liver (2780 g.):

Was considerably enlarged and tense with both lobes equally affected. On section the parenchyma was orange-yellow in colour and the normal lobular markings were seen with difficulty.

Microscopically (3 sections): There was very marked fatty change in all the liver cells with the exception of a few cells around portal tracts where the changes were less marked. The portal tracts appeared decreased in number and central veins could not be recognised so that the lobular pattern was not identified. A few thin strands of fibrous tissue were noted extending from the portal tracts and occasionally enclosing small groups of liver cells. The portal veins were slightly distended and the liver cells showed no evidence of excessive activity.

Comment:

The histological changes in this case suggest that this is a very early case of a diffuse hepatic fibrosis associated with marked fatty infiltration of the liver and with alcoholism. Death probably occurred independently of the condition of the liver.

Case No. 8

213/48. Male, aet. 57. Occupation: civil servant.

History:

The patient's abdomen had been grossly swollen for some time before death and had been tapped on repeated occasions. His liver was palpable 3 fingers breadth below the costal margin and a firm rubbery mass was present in the left axilla. Death was due to extensive Hodgkin's disease and a markedly cirrhotic liver was also present.

Liver (2260 g.):

The capsule was slightly thickened, the liver heavily bile-stained, and coarsely nodular. No lymphadenoma was present on naked-eye examination.

Microscopically: There was complete loss of normal hepatic architecture, no normal lobules being visible. Many thin strands of fibrous tissue intersected the tissue dividing it into nodules of varying sizes, some of them moderately large. The fibrous tissue contained many small bile channels, capillaries, small clumps of liver cells in some places and a moderate number of lymphocytes. There were scarcely any fatty changes in the liver cells and many double nucleated forms were present. No definite central veins were identified. The portal veins in some areas were considerably distended.

Comment:

This case is complicated by the presence of Hodgkin's disease. There is no indication as to which type of cirrhosis it originally belonged.

Case No. 9

216/48. Female, aet. 72. Occupation: housewife.

History:

The patient suffered from hypertension and was admitted with a left hemiplegia due to a pontine haemorrhage. For 4 months before this the patient had suffered from diarrhoea and constipation, and though X-ray examinations of the alimentary tract were negative, the liver was noted to be palpable.

Liver /

Liver (1216 g.):

Was noted only as showing well marked c.v.c. and probably some fatty change.

Microscopically (1 section): The hepatic cells all showed marked autolytic changes, and considerable fatty changes were observed in a few cells scattered throughout the lobules. There was some tendency for the portal tracts to occur in small groups and in no place could completely normal architecture be identified. There was a slight increase in the number of bile ducts present in one or two of the portal tracts and many of the liver cells contained two nuclei.

Comment:

Though it is difficult in view of the amount of autolysis present in the section to study the slide in much detail, the general appearance of clumping of the portal tracts and the apparent distortion of the lobular architecture suggests that there is an early cirrhosis present. This theory is substantiated by the presence of regeneration and activity in the liver cells. Associated with this picture there is a possible chronic venous congestion caused by a failing hypertensive heart.

Case No. 10

229/48. Female, aet. 75. Occupation: housewife.

History:

This patient had been known to suffer from diabetes mellitus for many years. There had been vomiting for one week before death, with the passage of no fluid or flatus. On the day of death the patient had a large haematemesis from an eroded vessel in the base of a large prepyloric ulcer. At autopsy fibrosis of the liver and pancreas was present.

Liver (1280 g.):

Was noted to show a moderate fine granularity in which the normal architecture was difficult to distinguish.

Microscopically (1 section): There was marked clumping of the portal tracts and complete loss of normal lobular architecture. Many of the portal tracts had radiating cords of liver cells running from them, but these cords quickly lost their regular arrangement. A slight /

slight degree of fatty change was present in scattered cells and there were also several small areas of necrosis of small groups of liver cells in which there was some polymorphic infiltration and haemorrhage. Many liver cells contained two nuclei and others showed considerable variation in nuclear size. The portal tracts contained a slight excess of fibrous tissue with infiltration by a few small round cells and fairly numerous proliferated bile ducts. The central veins were still visible in many places and there was no fibrosis around them. There were well-marked hyaline changes in the small branches of the hepatic artery.

Comment:

Here again there is clumping of the portal tracts, loss of normal architecture and evidence of regenerative processes. Long-standing chronic congestion was also possibly present.

Case No. 11

251/48. Male, aet. 47. Occupation: railway clerk.

History:

For 3 years before death there had been increasing weakness and loss of weight with, during the last two months, increasing oedema of ankles, ascites and jaundice.

Liver (1000 g.):

There was slight wrinkling of the capsule with mottling of the cut surface, bile staining and numerous small haemorrhages.

Microscopically (2 sections): There was marked disruption of the lobular architecture and intersecting the parenchyma there were numerous thick strands of collagenous fibrous tissue containing many small proliferating bile ducts and some lymphocytes. The areas of liver tissue remaining varied greatly in size but were often very small, containing only a few liver cells. Many of the liver cells in these nodules contained double nuclei but they showed no evidence of fatty infiltration. The bile ducts were dilated and collapsed.

In one section the process appeared more active, with no definite nodular formation, the collagenous tissue infiltrating and spreading into the parenchyma rather than growing around nodules. The capillaries everywhere were very congested and round cell collections, where present, /

present, consisted mainly of lymphocytes with a few plasma cells and an occasional polymorph. In a few areas there were small patches of acute congestion in the vicinity of which there appeared to have been recent cell death.

Comment:

The appearances are those of an actively progressing lesion on which recent more acute terminal changes had supervened. There is no evidence on which it could be decided to which group of cirrhosis this case belonged.

Case No. 12

267/48. Male, aet. 77. Occupation: retired.

History:

The patient lived alone and had been complaining of constipation and difficulty in micturition. On admission he was unco-operative and semi-conscious. Death was due to an acute urinary infection, myocardial fibrosis and hypertension.

Liver (1460 g.):

Was noted as showing a slight fine nodularity.

Microscopically (2 sections): There was very marked infiltration of the portal tracts by small round cells and one or two polymorphs. There was also slight proliferation of bile ducts, but no very marked increase in the amount of fibrous tissue around the portal tracts. There was well-marked distortion of the normal lobular pattern, many liver cells containing double nuclei. The hepatic artery showed occasional medial hyaline changes and throughout the parenchyma were scattered a few small groups of polymorphonuclear leucocytes. Several central veins were identified amongst the liver cells.

Comment:

It is impossible to say to what type of cirrhosis this case belongs. It can be noted only that he lived alone and that from the history and the findings at post mortem examination considerable chronic venous congestion can be assumed to have been present. Fibrosis was not marked.

Case No. 13

279/48. Male, aet. 48. Occupation: baker.

History:

About 5 months before death the patient had a large haematemesis followed by the development of ascites. Lieno-renal anastomosis was performed but the patient became shocked and despite energetic measures died of cardiac failure. He was known to be of alcoholic habits. He was jaundiced for 3 weeks when aged 18.

Liver (1160 g.):

The organ was irregularly nodular, the nodules varying from 0.5 to 1.0 cm. in diameter. The right lobe was more reduced in size than the left lobe, and the quadrate lobe was unusually prominent. The liver was sent uncut to the Department of Surgery.

Microscopically (1 section): The hepatic artery and portal vein had been injected with neoprine latex so that there was slight distortion of the parenchyma with dilation of small groups of sinusoids. Not all the central veins had been filled by the injection and many were still full of R.B.Cs. Around most central veins there was a thin layer of fibrous tissue and the cells radiating from them showed a fairly well-marked regular arrangement. A similar regular arrangement of cells was noted around portal tracts but no completely normal lobule was observed, and though there was no excess of fibrous tissue present around the portal tracts, there was considerable distortion of the normal lobular architecture. There was no obvious activity of the liver cells, a few of which showed slight fatty changes.

Comment:

The main feature of interest here is the complete absence of any fibrous tissue reaction although a definite cirrhosis is present. It is interesting to note that the patient, besides showing a definite alcoholic tendency, also suffered as a young man an attack of what may have been infective hepatitis.

Case No. 14

302/48. Female, aet. 72. Occupation: housewife.

History: /

History:

The patient had been mildly diabetic for 5 years. For about 5 days before death she had complained of a mild respiratory infection. She was brought into hospital in coma and death was found to be due to coronary thrombosis and a cerebellar infarct.

Liver (1300 g.):

The left lobe was very slightly nodular with marked chronic venous congestion throughout both lobes.

Microscopically (2 sections): Except that the chronic venous congestion was more marked in the section from the right lobe, both sections showed similar changes. There was a slight increase in the amount of fibrous tissue around the portal tracts and also early bile duct proliferation. The portal tracts were slightly clumped and there was slight distortion, especially in the left lobe, of the normal lobular architecture though a few fairly normal areas could be identified. The liver cells showed evidence of considerable activity, some of them containing 3 or 4 nuclei; others showed slight fatty changes. Central veins could be easily identified and early collagenous changes were present around them.

Comment:

There is some clumping of the portal tracts, lobular distortion and evidence of liver cell activity all combined with well-marked chronic venous congestion.

Case No. 15

367/48. Male, aet. 29. Occupation: builder.

History:

Six weeks before admission the patient complained of chest pain, then ascites with symptoms of intestinal obstruction. After paracentesis a mass was palpable in the right side of the abdomen.

Liver (3800 g.):

The right lobe was especially enlarged and the whole organ irregularly nodular, most of the nodules being more than 1 cm. in diameter. Through the right lobe there were also many small white tumour masses. The cirrhotic nodules were demarcated by well-marked bands of fibrous tissue.

Microscopically /

Microscopically (6 sections): Three main pictures were present: (1) small clumps of highly malignant hepatic cells occurring in large masses and occasionally merging into (2) rather pale staining, very active-looking liver cells containing many double nuclei and showing marked variation in nuclear size, no regular lobular arrangement and surrounded by thin but well-formed bands of fibrous tissue; (3) more normal-looking liver cells also showing an excess of nuclear activity and arranged in irregular cords. Around the nodules of these three different cell types were well-formed bands of fibrous tissue containing a few small proliferated bile ducts. Throughout the nodules of pale staining and more normal-looking liver cells, portal tracts and central veins could be identified, and in one place one normal lobule was made out though elsewhere the normal lobular architecture was completely lost.

Comment:

This is a case of carcinoma of the liver, and in view of the naked-eye appearance of the liver and the presence of at least one normal lobule in the sections examined, this carcinoma would appear to be superimposed on a liver the seat of previous post-necrotic scarring.

Case No. 16

475/48. Male, aet. 19. Occupation: painter.

History:

Three months before death the patient had a large haematemesis which was followed by the onset of oedema of his ankles and rapidly increasing ascites. Lienorenal anastomosis was performed but the patient developed signs of a left cerebral thrombosis and died 5 days after operation. He had no history of contact with chemicals or preceding jaundice. He was not noted as being alcoholic.

Liver (1180 g.):

Was decreased in size but was of normal shape. Both lobes were nodular, the nodules being about 1 cm. in diameter and being surrounded by well-formed fibrous bands.

Microscopically (3 sections): Wide bands of fibrous tissue intersected the sections. They contained numerous small bile ducts and many lymphocytes. In many places small groups of liver cells had become engulfed in this fibrous tissue which surrounded quite large, /

large, well-defined nodules of liver cells devoid of any normal architectural arrangement. There was little fatty change in any of the liver cells and little evidence of undue activity in them. In these nodules a few central veins were seen but there was no normal arrangement of cells around them. In one section a few small areas of necrosis and haemorrhage were seen in the centres of these nodules - probably anoxic in origin.

Comment:

Except that there are well-formed bands of fibrous tissue present throughout the liver, there is no clue as to the type of cirrhosis to which this case belongs. The main point of interest is the complete absence of a possible cause for the cirrhosis of the liver.

Case No. 17

513/48. Male, aet. 53. Occupation: excise watcher.

History:

The patient was admitted two days before death. He was comatose and markedly jaundiced.

Liver (1100 g.):

Was diffusely and evenly cirrhotic, the nodules being about 1 cm. in diameter and the changes being similar in both lobes.

Microscopically (2 sections): The parenchyma was divided up into nodules of varying size, mainly fairly small, by thick bands of fibrous tissue containing numerous small bile ducts, capillaries and small round cells. In the nodules of liver cells no normal lobular architecture was visible, and in the centres of many of the nodules in the section from the right lobe there were many areas of fibrosis, presumably evidence of previous ischaemic damage, for they appeared to have no connection with the fibrous tissue around the outsides of the nodules. Central veins were rarely recognised. A few hepatic cells showed a moderate degree of fatty infiltration but no marked nuclear activity.

Comment:

This is another case of indeterminate type. The main point of interest in it is the presence of changes taken to indicate the occurrence of previous periods of anoxia. /

anoxia. This patient acts to some extent as a control case to the cases of diffuse hepatic fibrosis, for although he was admitted in coma two days before death, his liver cells do not show a marked fat content.

Case No. 18

528/48. Female, aet. 62. Occupation: housewife.

History:

The patient had been feeling "out of sorts" for 6 weeks with jaundice for 2 weeks and ascites for 4 days. She had never previously suffered from jaundice.

Liver (1120 g.):

Was finely and evenly nodular, the changes affecting both lobes equally. The organ was tough and fibrous, exhibiting on section a nodular appearance with a dark green fibrous background.

Microscopically (2 sections): Post-mortem autolysis appeared to be well-marked; it could be seen, however, that the parenchyma was divided up by strands of fibrous tissue of a largely collagenous structure - one or two bands being very thick. This fibrous tissue contained many thin-walled capillary spaces and scattered collections of lymphocytes. In some places it sent thin collagenous offshoots into the nodules of surviving liver cells. These nodules were mainly small in size and showed no normal lobular pattern. Central veins were only occasionally seen and the striking feature of the liver cells was the possession, mainly by cells at the periphery of the nodules, of small brown pigment granules - probably lipochrome originating from previously damaged liver cells. In the centre of some nodules there were small areas of haemorrhage and necrosis.

Comment:

This is yet another case of cirrhosis of indeterminate origin. The terminal process appears to have been fairly acute, involving extensive death of liver cells, and to have produced a picture a little similar to that seen in fatal cases of infectious hepatitis, though here there is more evidence of an old-standing lesion. It should be noted that there has been in this case no previous attack of infectious hepatitis.

Case No. 19

542/48. Male, aet. 24. Occupation: Ex R.A.F.

History:

The patient gave a history of a large haematemesis 2 years before death and of another 18 months later. A lieno-renal anastomosis was performed but a left haemo-thorax and peritoneum developed along with torsion of the anastomosis and he died 4 days after the operation.

Liver (1860 g.):

Was finely granular with no obvious coarse fibrosis. On section small areas of necrosis were seen scattered throughout the parenchyma.

Microscopically (2 sections): Though one normal lobule was identified in the section from the right lobe, further normal lobular architecture could not be made out and the normal relationship of portal tracts to central veins was lost. A few central veins were visible with short radiating strands of liver cells running from them. The portal tracts showed only a slight excess of fibrous tissue, occasionally a few scattered lymphocytes and a few extra small bile ducts. Though occasional strands of thin fibrous tissue ran out from the portal tracts, an excess of fibrous tissue was not a feature of this case. The liver cells showed no evidence of excessive activity but only rather diffuse quite well-marked fine fatty vacuolation. Scattered throughout the section from the left lobe were many well-marked areas of anoxia into which slight haemorrhage had occurred.

Comment:

In view of the finding of a normal lobule in what is otherwise a cirrhotic liver, this case must be classified as one of post-necrotic scarring. The history gives, however, no clue as to its possible etiology. It is interesting to note that the ischaemic changes are much more marked in the section from the left lobe.

Case No. 20

549/48. Female, aet. 37. Occupation: assistant in drysalts.

History /

History:

Apart from "severe anaemia" in childhood, the patient had had no previous illnesses. Two months before death she developed oedema of the ankles, then ascites and jaundice. There was no history of any dietary deficiency, of chemical contacts, apart from her work in a drysalter's, or of previous jaundice.

Liver (820 g.):

The organ was not greatly distorted but was coarsely nodular. The nodules were of equal size in both lobes. On section large areas of the parenchyma were deeply bile-stained.

Microscopically (2 sections): The parenchyma was divided into nodules of varying size by broad, well-formed bands of fibrous tissue which contained numerous congested capillaries, many poorly-formed bile ducts or small clumps of liver cells, and small groups of lymphocytic infiltration. These bands occasionally penetrated the nodules of liver cells and further subdivided them. No normal lobules or suggestion of normal lobules were seen except in the section from the left lobe where a central vein was identified around which the liver cells had a radial arrangement. The liver cells showed no fatty changes or evidence of undue nuclear activity.

Comment:

The process seen here is active-looking and probably not of very long duration - there is no indication as to what type of cirrhosis this case is related.

Case No. 21

565/48. Female, aet 51. Occupation: housewife.

History:

Six months before her admission the patient had jaundice, this resolved but recurred 6 weeks before her death. Clinically the jaundice was thought to be obstructive in origin. For the 10 days before death ascites and some vomiting had been present.

Liver /

Liver (1260 g.):

Was noted as being moderately nodular, the nodules varying between $\frac{1}{2}$ -1 cm. in diameter. On section the parenchyma showed a rather indistinct, yellow small nodularity (0.3 cm. in diameter). Both lobes were affected equally.

Microscopically (5 sections): There was complete loss of the normal lobular architecture, the parenchyma being composed of small nodules of irregularly arranged liver cells surrounded by thick bands of fibrous tissue. These bands contained many isolated liver cells, small bile ducts and areas of small round cells, mainly lymphocytes. The nodules of liver cells were intersected and further subdivided by many active-looking collagenous bands of fibrous tissue growing in from the edge of the nodule. The bands of fibrous tissue were notably thick below the capsule. The liver cells showed no fatty changes or evidence of activity.

Comment:

Here again there is no evidence which would allow of a decision being made as to which group of cirrhosis this belongs. The most interesting feature is the extent to which the liver cells have been encroached on by the bands of fibrous tissue.

Case No. 22

566/48. Female, aet. 63. Occupation: Housewife.

History:

The patient suffered from mitral stenosis and had complained of breathlessness for 3 months and of oedema for 2 months. She had been slightly jaundiced for one week.

Liver (1100 g.):

Was noted as showing chronic venous congestion.

Microscopically (2 sections): There was some clumping of the portal tracts with a slight excess of fibrous tissue around them so that they were more prominent than usual. This fibrous tissue did not, however, stream out into the surrounding tissue. Around many of the central veins there was a slight increase in collagen and the sinuses around the central veins were markedly distended by R.B.Cs. Though central veins /

veins were readily recognised and the liver cells were still arranged in well-defined cords, the normal relationship of the central veins to the portal tracts was lost. Many of the hepatic cells showed slight fatty changes.

Comment:

There is definite distortion of the normal lobular architecture with both clinical and pathological evidence of chronic venous congestion being present.

Case No. 23

600/48. Male, aet. 60. Occupation: retired motor inspector.

History:

The patient had shown increasing weakness and drowsiness. On admission he was disoriented and a diagnosis of uraemia was made.

Liver (1000 g.):

The left lobe was markedly atrophied and was reduced to a small tag 3 cm. x 1 cm. in size. The right lobe was slightly nodular, the nodules measuring about 1 cm. in diameter, and it was described as presenting the typical appearance of a portal cirrhosis. The umbilical vein was patent and joined the left branch of the portal vein.

Microscopically (2 sections, both from right lobe): The liver parenchyma was composed of large nodules of liver cells separated by thin bands of fibrous tissue containing a few scattered lymphocytes and small bile channels. The cells forming the nodules showed considerable variation in nuclear size and many double nucleated forms were present. They formed rather irregular cords so that though portal tracts and central veins could be easily identified in these nodules, only in one small area was the architecture normal. Occasional small clumps of lymphocytes and polymorphs were present throughout the sections.

Comment:

The association of the patent umbilical vein and the atrophy of the left lobe which was reduced to a mere fibrous tag is of interest. The presence of a normal lobule in one section places this case in the group of post-necrotic scarring.

Case No. 24

614/48. Male, aet. 44. Occupation: works foreman.

History:

The patient had repeated large haematemeses during the two years before death. Lieno-renal anastomosis was performed but the patient died 4 days later from a further massive haematemesis.

Liver (1440 g.):

Was diffusely nodular with the left lobe slightly diminished in size. On section the parenchyma was pale and seen to be composed of small nodules less than 1 cm. in diameter surrounded by bands of fibrous tissue.

Microscopically (2 sections): The parenchyma was divided into nodules of varying sizes by thin strands of fibrous tissue which in places penetrated the nodules of liver tissue and further subdivided them. The fibrous tissue contained large numbers of lymphocytes and a few widely dilated capillary channels. Small clumps of lymphocytes and areas of fibrous tissue were also noted throughout the nodules. These nodules were composed of very active cells arranged in irregular cords so that though one or two central veins were identified, no further trace of a lobular architecture could be made out. The liver cells showed marked variation in nuclear size and shape, and double nucleated forms were common.

Though the picture in both lobes was essentially similar, there was more cellular activity and less fibrosis in the section from the left lobe.

Comment:

This is yet another indeterminate case where it is impossible to decide to what group it belongs.

Case No. 25

615/48. Male, aet. 40. Occupation: bus driver.

History:

The patient had an attack of jaundice in 1935 and another attack 11 weeks before admission. On admission there was marked ascites and some oedema.

Liver /

Liver (1100 g.):

Was small, pale and firm with a nodular surface. On section these nodules were seen to vary a little in size, the largest being about 1 cm. in diameter. There was no obvious excess of fibrous tissue around them, but a large area of liver tissue at about the junction of the right and left lobes was completely fibrotic.

Microscopically (2 sections): The parenchyma was divided into small nodules of varying sizes by strands of fibrous tissue. In many places these strands were thin and well-defined, while in other places they were ill-defined and straggled out into the nodules of liver cells. They were densely infiltrated with lymphocytes and many small bile ducts were also present along with numerous small capillary spaces. No normal lobular arrangement or central veins could be identified. The liver cells showed slight irregularity in nuclear size and a few double nucleated forms were present.

In this case, as in the previous one, the section from the left lobe showed slightly less fibrosis and much more marked nuclear activity. In the section from the left lobe a few central veins but no lobular architecture were observed.

Comment:

In spite of the indeterminate nature of the histological picture, the large area of scarring present in the organ would seem to suggest that this cirrhosis was due to post-necrotic scarring.

Case No. 26

54/49. Female, aet. 64. Occupation: housewife.

History:

The patient was admitted with a history of increasing swelling of the abdomen. She was a known alcoholic.

Liver (1000 g.):

Was pale, shrunken and diffusely nodular, the nodules varying from 2 to 6 mm. in diameter. There was no bile staining and on section the nodularity was seen to extend evenly through the parenchyma.

Microscopically /

Microscopically (2 sections): The parenchyma was divided up into small nodules by well-defined, but in no place very thick, bands of fibrous tissue. These bands contained many distended vascular spaces, small, poorly-formed bile ducts and a slight, diffuse small round-cell infiltration. The nodules of liver cells were made up of columns of liver cells showing no normal lobular arrangement though a few spaces were seen in them which were taken to be central veins. One or two small portal tracts were also present. The liver cells showed evidence of slight nuclear activity while in a few nodules fatty changes were well-marked.

Comment:

This again is an indeterminate case though the naked-eye appearance along with the history of alcoholism would suggest that this might be called a diffuse hepatic fibrosis.

Case No. 27

75/49. Female, aet. 54. Occupation: housewife.

History:

The patient was known to suffer from mitral stenosis and she had been out and in of cardiac failure "for years".

Liver (1340 g.):

Was firm and pale with a finely granular surface and on section there was marked nutmeg mottling of the parenchyma.

Microscopically (1 section): There was some upset of the normal lobular architecture in which the portal tracts showed a slight tendency to clump and to be unduly prominent. This prominence was probably due to the slight increase in the amount of fibrous tissue around them and to slight bile duct proliferation. The central veins, though distended, showed no obvious abnormality; few could be distinguished. Almost all the sinusoids showed well-marked distension while in the centres of groups of liver cells small areas of necrosis, fatty changes and haemorrhage were present. The liver cells showed no evidence of undue activity. The lack of easily identified central veins and the clumping of portal tracts gave an appearance of considerable distortion of the normal architecture.

Comment /

Comment:

The appearance of upset of the lobular architecture associated with the very long-standing history of chronic congestion suggest that the mild cirrhosis present in this case is a "cardiac" cirrhosis.

Case No. 28

79/49. Female, aet. 39. Occupation: not known.

History:

The patient was known to have mitral stenosis and aortic incompetence. She was admitted in congestive failure with gross ascites, and during the last 2 weeks of life developed well-marked jaundice.

Liver (about 700 g.):

The right lobe of the liver was rounded and coarsely nodular, many of the nodules being more than 1 cm. in diameter and all the nodules being surrounded by thin bands of fibrous tissue. The left lobe was represented by a small nodular flattened leaf of tissue 3 cm. x 2 cm. in size.

Microscopically (2 sections): The parenchyma was divided up into nodules of varying sizes by well-formed bands of fibrous tissue which contained small, well-formed bile ducts, and capillary spaces but no definite round-cell infiltration. Throughout the nodules of liver cells many small portal tracts were identified and though in one place a fairly normal lobule was seen in the section from the right lobe, elsewhere there was well-marked distortion of the lobular architecture. In several small areas the cellular staining was indistinct - probably small ischaemic areas.

Comment:

The naked-eye appearance of the liver and the finding of a normal lobule would suggest that this is a case of post-necrotic scarring. The general histological picture, however, coupled with the history of long-standing congestion, suggest also that there may be a "cardiac" basis to the cirrhosis.

Case No. 29

95/49. Female, aet. 54. Occupation: housekeeper.

History:

About 2 months before her death the patient had an attack of infective hepatitis. This cleared up slightly but the jaundice recurred and steadily deepened.

Liver (1600 g.):

Was large and soft with numerous small subcapsular haemorrhages. On section the cut surface was uniformly pale and yellow so that the lobular architecture could not be made out. A few small haemorrhagic areas were noted near the lower borders.

Microscopically (2 sections): No normal liver architecture was seen, the parenchyma being divided up into small groups of very autolytic-looking liver cells by numerous thin collagenous strands which appeared to run mainly around and from portal tracts and central veins, often isolating single liver cells. The picture was that of acute liver damage, probably continued for some time before death and with little evidence of repair.

Biopsy (2 weeks before death): There was some centrilobular necrosis with centrilobular and portal tract cellular reaction. The lobular framework was well preserved. Many portal tracts contained active-looking fibroblasts.

Comment:

The histological picture in this case is that of acute liver necrosis following an attack of infective hepatitis.

Case No. 30

L.H.A. 387. Male, aet. 56. Occupation: not known.

History:

The patient had felt unwell for about 6 weeks before his death and had developed jaundice. Death was due to carcinoma of the stomach with spread to the liver.

Liver /

Liver:

Was reduced to two-thirds its normal size and was grossly nodular, the nodules in the left lobe being slightly smaller than those in the right, and on section they were seen to be surrounded by thin bands of fibrous tissue, the largest nodules being 2-3 cm. in diameter. Local spread of the carcinoma from the stomach was present.

Microscopically (5 sections): The parenchyma was divided up into nodules of varying sizes by thick, well-formed bands of fibrous tissue which were irregularly present throughout the section. The fibrous tissue contained many small bile ducts and some small round cells. The nodules of liver cells which remained were further broken up by the presence of many small areas of necrosis - often most marked where bile plugs were most frequent - and small areas of fibrosis containing numerous small bile ducts. No trace of normal lobular architecture remained. The liver cells showed no evidence of nuclear activity.

Comment:

Though no normal areas were seen, the naked-eye appearance suggests that this is a case of post-necrotic scarring. Secondary changes have so changed the picture here that it is doubtful if any normal areas would be found no matter how many sections were examined.

Case No. 31

M.H.A. 3076. Male, aet. 46. Occupation: army officer

History:

The patient gave a history of indigestion for several years, then two days before admission he complained of severe abdominal pain and developed jaundice. His gall-bladder was removed and the bile ducts drained, but he died a few days later.

Liver (1030 g.):

Was coarsely nodular except over the inferior surface where an area of smooth softer tissue was present. The cut surface was deeply bile-stained and composed of small nodules, all less than 1 cm. in diameter and surrounded by well-formed bands of fibrous tissue.

Microscopically /

Microscopically (2 sections): The parenchyma was intersected by moderately thick bands of fibrous tissue containing many small round cells, a few small bile ducts and composed of active-looking fibrous tissue. The nodules of liver cells were often further subdivided by ingrowths of fibrous tissue and were mainly small in size. No areas of normal architecture could be made out. The liver cells occasionally showed slight fatty change and the majority of them contained small brown pigment granules. Many bile plugs were also seen but there was no reaction around the larger bile ducts.

Comment:

This is again an indeterminate type of cirrhosis associated apparently with long-standing biliary obstruction.

Case No. 32

475/47. Female, aet. 46. Occupation: hotel keeper.

History:

There had been increasing swelling of the abdomen for 3 months, associated with weakness.

Liver (1150 g.):

Was shrunken and grossly nodular, the nodules measuring up to 1 cm. in diameter and being surrounded by well-defined bands of fibrous tissue.

Microscopically (1 section): The parenchyma was divided up into nodules by bands of fibrous tissue. These bands varied in size and contained a few lymphocytes and small bile ducts, the larger bands sometimes enclosing small groups of liver cells. The nodules of liver cells, some of which were of quite large size, were composed of irregularly arranged columns of liver cells showing no normal lobular arrangement though one or two central veins were identified. Scattered areas of liver cells showed slight fatty changes. There was no evidence of undue nuclear activity.

Comment:

Apart from the naked-eye appearance which was typically that of a diffuse hepatic fibrosis, there is no indication as to what type of cirrhosis this case belongs.

Case No. 33

591/47. Female, aet. 74. Occupation: housewife

History:

The patient was discovered semi-conscious 60 hours before death. Coma developed and she died - death being due to a cerebral haemorrhage.

Liver (1300 g.):

Was slightly diminished in size with a relatively enlarged left lobe. There was slight even nodularity of the surface and the cut surface. The cut surface was markedly greasy.

Microscopically (1 section): The parenchyma was divided into small nodules by strands of fibrous tissue containing a few bile ducts, scattered lymphocytes and plasma cells. These strands of fibrous tissue were thin and grew out from around portal tracts, invading the surrounding parenchyma and in some places still further subdividing the nodules. Occasional central veins showing slight fibrosis around them were identified. The liver cells showed gross fatty changes throughout and many of the cells also contained double nuclei or showed marked variation in nuclear size.

Comment:

The picture here of fibrosis around the portal tracts and central veins along with such marked fatty changes is that of a diffuse hepatic fibrosis. Death in this case was not directly attributable to the liver condition.

Case No. 34

391/48. Male, aet. 62. Occupation: labourer.

History:

The patient had complained of a chronic cough for many years and died of broncho-pneumonia and pulmonary fibrosis.

Liver /

Liver (1540 g.):

There was no obvious naked-eye abnormality except for a slight constriction between the right and left lobes.

Microscopically (1 section): There was a slight increase in the amount of fibrous tissue around the portal tracts, which showed a suggestion of clumping. Along with the increase in fibrous tissue there was a fairly marked lymphocytic infiltration and slight bile duct proliferation. The fibrosis was most marked immediately below the capsule where strands of fibrous tissue infiltrated and subdivided liver lobules. In many places normal liver architecture was still visible though in others there was definite distortion. Around a few of the central veins there was a slight excess of collagen and fibrous tissue, and also centrilobular congestion. A few liver cells contained double nuclei.

Comment:

The histological appearance here is that of an early "cardiac" cirrhosis - a finding borne out by the history of possible long-standing congestion.

Case No. 35

59/49. Female, aet. 46. Occupation: not known.

History:

There was a history of long-standing hypertension with terminal broncho-pneumonia.

Liver (2250 g.):

Was smooth and on section there was no obvious chronic venous congestion, the surface being a uniform dusky red brown in colour.

Microscopically (1 section): There was some clumping of the portal tracts which also showed slight proliferation of bile ducts and arterioles. Though a normal arrangement of liver cords running from portal tracts to a central vein was observed in a few places, in general the normal lobular architecture was lost. The sinusoids were distended and congested as were the central veins where the latter were recognised. The liver cells showed slight evidence of nuclear activity and a few showed some fatty change.

Comment /

Comment:

The appearance here again is that of an early "cardiac" cirrhosis - a finding which the history would appear to substantiate.

Case No. 36

E.H.A. 839. Male, middle-aged. Occupation: not known.

History:

The patient was admitted to hospital with acute asthma, developed broncho-pneumonia and died.

Liver:

Was decreased in size, the left lobe more so than the right. There was uniform irregularity of the surface and on section the parenchyma was composed of clearly defined small nodules surrounded by scar tissue.

Microscopically (2 sections): The parenchyma was divided into nodules of varying sizes by thin strands of fibrous tissue formed of mature-looking fibrous tissue containing many small round cells, small bile canaliculi and small vascular spaces. In a few places very thin strands of fibrous tissue further intersected the nodules in which, though a few central veins could be recognised, no normal arrangement of liver cell columns could be made out. A few double nuclei were seen in liver cells near the periphery of the nodules.

Comment:

There is no indication as to the type of cirrhosis to which this case belongs.

Case No. 37

M.H.A. 3078. Female, aet. 79. Occupation: housework.

History:

At the age of 19 the patient had an attack of painless jaundice which lasted for one month. When 59 she had an attack /

attack of biliary colic with removal of a gall-stone. Jaundice and the symptoms recurred over the course of the next two years. Painless jaundice and ascites were present during the last few months of life.

Liver:

Was noted as being small, bile-stained and finely granular, the nodules measuring 5-7 mm. in diameter and being surrounded by thin strands of fibrous tissue.

Microscopically (2 sections): No normal lobules were seen, the parenchyma being divided into nodules of varying sizes by thick strands of fibrous tissue containing many small round cells, small bile canaliculi and scattered portal tracts. In a few places these strands of fibrous tissue penetrated to the centre of the nodules of liver cells. A few double nuclei and slight fatty changes were seen in scattered liver cells.

Comment:

There is no indication as to the type of cirrhosis to which this case belongs.

Case No. 38

Li. 1408. Male, aet. 27. Occupation: army officer.

Biopsy Specimen

History:

The patient had been known to have an enlarged liver and spleen for a year or two before his admission. In August 1947 he had severe recurrent haematemesis and a month later a lieno-renal anastomosis was performed. The patient remains alive and well.

Liver:

Was noted at operation to be shrunken and grossly cirrhotic. The pressure in the portal vein was 250 mm. of water.

Microscopically: No liver parenchyma was present in the superficial portion of the section, though throughout the deeper parts small nodules of liver cells without any lobular arrangement were present. These liver nodules showed marked nuclear activity of the peripheral cells and they were invaded by thin bands of fibrous tissue and /

and small round cells. Around these nodules there were bands of thick fibrous tissue containing well-defined portal tracts and, most marked in the subcapsular area, many well-formed widely dilated vascular spaces. Small bile canaliculi were also present along with a scattered small round cell infiltration. The dilated vascular spaces probably represented widely patent collateral channels.

Comment:

This is a moderately active-looking cirrhosis in which there is no clue as to the type to which it belongs.

Case No. 39

Lii. 32. Male, aet. 29. Occupation: German P.O.W.

Biopsy Specimen

History:

Six years ago the patient had an attack of infectious hepatitis, the jaundice recurring a few weeks later and again several times over the next few months. About 19 months ago he had a small haematemesis and lieno-renal anastomosis was performed. So far as is known, the patient remains alive.

Liver:

Was noted at operation to have a grossly irregular surface covered by thick bands of fibrous tissue, the intervening parenchyma forming very prominent nodules.

Microscopically: The normal lobular architecture was completely lost, the parenchyma being composed of irregular columns of liver cells showing, many of them, double nuclei and considerable variation in nuclear size. Portal tracts were few in number and where present showed slight fibrosis and the presence of several widely distended capillary spaces. Scattered throughout the parenchyma were small areas of fibrosis and round cell infiltration with again a few widely distended capillary spaces. In a few places the sinusoids between the columns of liver cells were widely distended. Occasional hepatic veins were recognised.

Comment /

Comment:

This is another case of indeterminate type though the description of the liver would seem to indicate that it may be a case of post-necrotic scarring - a fact supported by the history.

Case No. 40

Lii. 1960. Female, aet. 64. Occupation: housewife.

Biopsy Specimen

History:

For about two years the patient had been feeling off colour. A few months before admission she became slightly jaundiced, her ankles and her abdomen began to swell and she complained of anorexia. Jaundice decreased and patient felt better.

Liver:

Was noted at operation to be uniformly nodular, the nodules being $\frac{1}{2}$ -1 cm. in diameter. The left lobe appeared to be slightly enlarged.

Microscopically: There was complete loss of the normal lobular architecture, the parenchyma being divided into small or often very large nodules of liver cells. Between these cells ran slightly dilated sinusoids, and between these nodules thin strands of fibrous tissue containing very numerous small bile ducts and heavily infiltrated by lymphocytes. The liver cells showed a few double nucleated forms and only slightly excessive activity. A few central veins were recognised. A section stained for fat showed a considerable amount of fat to be present in most liver cells, though this was not a feature of the H. and E. stained section.

Comment:

This is another case where the type of cirrhosis has not been determined.

Case No. 41

Liii. 640. Male, aet. 38. Occupation: publican.

Biopsy Specimen

History:

The patient had a large haematemesis a few weeks before admission. Previous to this, apart from a very small haematemesis in 1941, he had kept well. He had never had infective hepatitis, but at one period - after the first haematemesis - he worked with benzene and tri-chlorethylene. He died of portal vein thrombosis about 3 weeks after splenectomy.

Liver, at post mortem (not weighed):

Though the surface was not markedly nodular, it contained one or two clefts 1-2 cm. in depth. On section the parenchyma was seen to be composed of rather pale, ill-defined nodules $\frac{1}{2}$ -1 cm. in diameter with no obvious increase in fibrous tissue.

Microscopically (biopsy): No completely normal lobular architecture was seen, both the portal tracts and the central veins, especially the latter, showing an apparent decrease in number. The portal tracts showed only very slight fibrosis, a few small bile ducts and in one place a well-marked lymphocytic infiltration. Though a few fine strands of fibrous tissue intersected the parenchyma, there was no true nodular arrangement. The liver cells showed evidence of slight nuclear activity and around a few of the central veins the liver cells had a definite radial arrangement.

Comment:

From the naked-eye appearance, this would appear to be a case of post-necrotic scarring.

Case No. 42

Liii. 185. Male, aet. 27. Occupation: brewery worker.

Biopsy Specimen

History:

For about 6 months before his admission the patient had been becoming thinner and his abdomen distended. He had /

had never had jaundice or contact with chemicals. Until recently he had been a heavy beer drinker. Splenectomy was performed a few weeks ago and the patient is now convalescent.

Liver:

At operation the left lobe appeared normal; the caudate lobe was enlarged and the right lobe grossly nodular and fibrotic.

Microscopically: There was a fine fibrosis extending out from a few portal tracts to encircle fairly large nodules of liver cells. The portal tracts showed only a very slight increase in fibrous tissue and an occasional extra bile duct with a slight round-cell infiltration. This fibrous tissue reaction was not, however, a conspicuous feature of the section. The liver cells showed evidence of some nuclear activity, binucleate forms being fairly common. Though on the whole the lobular pattern was markedly distorted, two normal lobules were observed.

Comment:

From the presence of some normal lobular architecture, this case, in spite of the history of alcoholism, would appear to be one of post-necrotic scarring.

Case No. 43

Liii. 271. Male, aet. 20. Occupation: R.A.S.C.

Biopsy Specimen

History:

The patient had had three large haematemeses in the previous 7 months. He had noted himself to have "a bit of a paunch" for 3 years, but otherwise had kept well. He had never had jaundice but had on several occasions worked, with due precautions, using carbon tetrachloride. A lienorenal anastomosis was performed a few weeks ago, and the patient has made a good recovery from the operation.

Liver:

At operation it was noted to be the seat of definite but not severe cirrhosis, the surface being slightly nodular.

Microscopically /

Microscopically: The parenchyma was divided up into lobules of varying sizes by thin bands of fibrous tissue running out from portal tracts. The portal tracts showed a slight excess of bile ducts and a scanty round-cell infiltration. The liver cells in no place showed a normal lobular pattern and central veins were not often identified, though when they were they occasionally showed a radial arrangement of liver cells around them.

Comment:

This is another indeterminate case in which the type of cirrhosis is not known. If the date of the development of the paunch is of significance, it is of importance in that it occurred before the exposure to carbon tetrachloride.

Case No. 44.

Liii. 660. Male, aet. 26. Occupation: farm worker.

Biopsy Specimen

History:

Except that the patient had had four small haematemeses in the past 4 years, he had never been ill in his life. There was no history of any contacts with harmful chemicals. Splenectomy was performed a few weeks ago and the patient has remained well since.

Liver:

Was noted at operation to be small and to show a fine cirrhosis.

Microscopically: There was some distortion of the lobular pattern though in some places this was not very marked, many central veins being identified with radiating cords of liver cells running from them. No completely normal lobule was, however, seen. The portal tracts showed a very slightly increased fibrosis and a slight round-cell infiltration. The central veins were often unduly near portal tracts as if they were being displaced towards them by the cirrhotic process.

Comment:

This is another indeterminate case, the main point of interest being the complete lack in the history of any possible cause for the presence of the cirrhosis.

Summary of Findings

Adopting the criteria enumerated in the introductory paragraph, it has been found that:-

- (1) Three cases (Nos. 3, 7 and 33) show a diffuse hepatic fibrosis.
- (2) Eight cases (Nos. 15, 19, 23, 25, 28, 30, 41 and 42) show post-necrotic scarring.

Further study of the original group of cases enabled other small groups to be recognised:-

- (3) Seven cases of cardiac cirrhosis (Nos. 9, 10, 14, 22, 27, 34 and 35).
- (4) Two cases of infective hepatitis (Nos. 4 and 29).
- (5) Three cases of cirrhosis without fibrosis (Nos. 1, 2 and 13).

These groups of cases will be described in detail, but meanwhile it is noted that by splitting these off the original group of 44 cases, 21 cases of indeterminate type remain. Of these, in 11 cases (Nos. 5, 16, 17, 18, 20, 21, 24, 26, 32, 36 and 37) there was on naked-eye examination of the liver a diffuse nodular cirrhosis, the nodules being less than 1 cm. in diameter with no marked distortion of the liver - that is, they are probably examples of diffuse hepatic fibrosis.

The results will now be discussed in more detail.

After /

After this investigation was begun, it was found that Goldblatt (1947) had described an investigation carried out by eight well-known American pathologists in which 106 cases of cirrhosis of the liver were studied and an attempt made to determine in each case whether a diffuse hepatic fibrosis or post-necrotic scarring was the basis of the liver lesion. Using certain criteria, complete unanimity was reached in 30 out of 106 cases and in 70 out of 106 cases when unanimity was reached on six out of eight criteria.

TABLE I

Case No.	Weight of liver	Cause of death
1	780 g.	Liver failure
2	2780 g.	Broncho-pneumonia
3	1100 g.	Subarachnoid hemorrhage

In view of the basic similarity between the three cases, it would appear justifiable to assume that the smallest organ represents the end result of the same process as was present in the other two cases. This supposition is supported by the clinical history of the cases. For the patient with the largest liver died following an acute drinking episode, when presumably the cirrhosis was still at an early stage. The second case died of a subarachnoid hemorrhage, a factor in no way connected with the condition of the liver, the organ showing thicker bands of /

DISCUSSION

(1) Diffuse Hepatic Fibrosis

The common feature of these three cases is the marked distension of the liver cells by large single fat globules associated with the presence of fine strands of fibrous tissue running from the portal tracts and central veins. There is also definite distortion of the lobular architecture though this is difficult to make out, and although the histological picture is similar in all these cases there is a marked difference in the size of the organs.

TABLE I

Case No.	Weight of liver	Cause of Death
3	780 g.	Liver failure
7	2780 g.	Broncho-pneumonia
34	1300 g.	Subarachnoid haemorrhage

In view of the basic similarity between the three cases, it would appear justifiable to assume that the smallest organ represents the end result of the same process as was present in the other two cases. This supposition is supported by the clinical history of the cases, for the patient with the largest liver died following an acute drinking episode, when presumably the cirrhosis was still at an early stage: the second case died of a subarachnoid haemorrhage, a factor in no way connected with the condition of the liver, the organ showing thicker bands of /

of fibrous tissue and a more advanced process than in the previous case: the last case, that is, the one with the smallest liver, died of hepatic failure, and though in this case there is less fat present in the liver cells, this finding might be explained by the fact that on admission the patient received intravenous infusions of glucose.

That the administration of intravenous fluids should make this difference in the appearance of the liver cells underlines the fact that these three cases all died shortly after their admission to hospital, before administration of a hospital diet had an opportunity to improve the state of nutrition of the hepatic cells.

It has been recognised for many years that the amount of fat in a liver cell is not a dependable indication of the usual state of nutrition of that cell, for it has been shown experimentally that quite marked fatty changes can occur within a few hours of interference with their nutrition, either by metabolic means or by the administration of some appropriate toxic substance. As indicated above, an excess of fat can be removed almost as quickly when the nutrition of the cells improves again.

In the commentary on Case No. 17 fatty changes were noted throughout the section, superimposed, it was thought, on a rather indeterminate cirrhotic picture. On examination of the history the patient was found to have been admitted in coma so that either the hospital diet had had no chance to exercise a beneficiary effect on the state of nutrition of the liver cells, or else the period of coma and the consequent failure in food intake had produced this picture.

Pursuing /

Pursuing this idea in another direction, all the cases in the indeterminate group which possessed an evenly and diffusely nodular liver were scrutinised. It was found that all these cases had been in hospital for at least a few days, and often for some considerable time, before they died.

TABLE II

Case No.	Weight of liver	Duration of stay in hospital
5	1620 g.	Few days
16	1180 g.	2 months
17	1100 g.	2 days
18	1120 g.	Few days
20	820 g.	12 days
21	1260 g.	Few days
24	1440 g.	2 months
26	1000 g.	8 days
32	1150 g.	7 days
36	Small	4 days
37	Small	5 weeks

The question therefore arises, might not these be cases of diffuse hepatic fibrosis in which a period of improved nutrition in hospital has changed the picture so that, using the criteria adopted, they have not been recognised as such? Whether this is the case or not it does not seem possible, from the case material available, to tell, though in theory at least this would /

would appear a reasonable supposition. In the three cases which have been taken as definite cases of diffuse hepatic fibrosis, it is not easy to picture how they would appear histologically were the fat globules not present, and conversely it would be just as difficult to picture the result of superadded fatty changes on these cases with diffusely cirrhotic livers.

From the evidence available, therefore, it is not possible to do any more than to indicate the possibility of the above explanation being applicable to a few cases of this intermediate group. The cases which have not so far fallen into a definite category may represent cases in which there has been a mixed dietary deficiency present which gave rise to a complicated pathological picture, or else be due to the superimposition of one type on another (Davies, 1949). If this latter sequence did occur, it is considered by Himsworth (1947) that it would probably be the superimposition of a diffuse hepatic fibrosis on a pre-existing post-necrotic scarring. Complicating factors of blood supply may be of importance in carrying the cirrhosis past a stage at which a diagnosis into one or other of Professor Himsworth's two types of cirrhosis can be made. The probable importance of such factors will be discussed in Part V.

It has already been noted that though the ideas put forward in Professor Himsworth's monograph form a very tempting and reasonable basis on which to construct theories as to the mode of production of cirrhosis, the exact part these factors play in the production of human cirrhosis has yet to be substantiated. Marked fatty changes in the hepatic cells occur in many conditions in human pathology, and associated with them there may be atrophy /

atrophy of cells, thickening of reticulum and replacement fibrosis (Connor, 1938), but that this picture will give rise to a true cirrhosis is questioned by many, and in spite of experimental work in animals which would seem to show that this progression is possible, its actual occurrence in man remains to be proved.

Those who support the view that fatty changes in the liver cells may eventually give rise to cirrhotic changes in the liver point out (Himsworth, 1947) that cirrhosis of the liver, as well as being the possible sequel to previous fatty infiltration, may also be a sequel to infiltrations of other kinds, for example, in the lipoid storage diseases. The Gillmans (1944) from South Africa, Davies (1948) from East Africa, and Waterlow (1948) from the West Indies, have been able to show that where large fatty livers due to deficient protein intake are found to occur frequently, in these same regions the incidence of cirrhosis is also raised. Again, an excessive intake of alcohol in the absence of an adequate food intake is known to cause fatty infiltration of the liver. These facts, coupled with the long acknowledged relationship between alcoholism and cirrhosis of the liver (Table III), would seem to provide strong arguments in favour of a direct relationship between fatty changes and cirrhosis of the liver.

TABLE /

TABLE III

Relation between Cirrhosis of the Liver and Alcoholism

Ratnoff and Patek (1942):	Alcoholism present in 54% (386 cases)
Eppinger (1925):	" " " 42% (376 ")
Howard and Watson (1947):	" " " 22% (100 ")
Boles, Crew and Dunbar (1947):	" " " 66% (50 ")

The discrepancies in the percentages of alcoholics in these different series were probably due to the different social strata to which the patients in the various series belonged. Although the correlation of these factors is so definite, the final proof of their relationship is still lacking.

This last point has been taken up by Boles, Crew and Dunbar (1947), and appears to be the view taken by many clinicians and pathologists. Gyorgi (1946) pointed out that fatty infiltration of the liver cells due to metabolic upsets is a common finding in diabetic patients, and goes on to observe that cirrhosis of the liver is no more common in the diabetic than in the non-diabetic. Connor (1938) affirms, however, that cirrhosis is more common in the diabetic.

Such then is the position at present - what light if any do the three cases noted as showing the features of a diffuse fibrosis shed on it? If the three cases described at the beginning of this section do represent, as it has been suggested, different stages of the same process, this would appear to indicate that diffuse hepatic fibrosis in man may result from prolonged and unrelieved fatty changes in the liver due to deficiency /

deficiency of certain substances in the diet.

It has been shown by Morrison (1947) that adequate and energetic treatment of patients with cirrhosis of the liver by a good diet and the administration of choline and methionine greatly improves their general condition and expectation of life. This therapeutic evidence would also indicate that, as the numerous authors already quoted have suggested, in some cases of cirrhosis of the liver the basic cause is a dietary deficiency. The fact that the large tense liver with marked fatty changes in the cells is firm, often palpable and often associated with jaundice due to obstruction of the small intralobular bile canaliculi and may be mistaken for an enlarged and cirrhotic liver, has been pointed out by Connor (1938) as the ability of the palpating hand to feel a liver depends mainly on its consistence (Bloomfield, 1938). In the acutely swollen fatty liver, therefore, a possible source of error in assessing the results of treatment of cirrhosis of the liver by dietary methods is present, for, of course, adequate therapy will reduce such a liver to normal again.

(2) Post-necrotic Scarring

Using the criteria set out in the introduction to this chapter, eight cases were found to show post-necrotic scarring. In five of them (Nos. 15, 19, 23, 28 and 42) examination of the sections revealed the presence of a normal lobule in an otherwise cirrhotic liver, while in three, despite a careful search, no normal lobule was seen, but in view of the naked-eye appearance /

appearance of the organ they were also included in this category. In four of the cases (Nos. 15, 23, 28 and 42) the presence of the normal lobules confirmed a diagnosis which could also be made from the naked-eye appearance of the organ.

Except that it has proved possible by examining only two sections in three of the cases and five in another to find a normal lobule in four out of five cases, where the diagnosis of post-necrotic scarring had already been made from the naked-eye appearance, little further comment on this group will be made. That these findings fit in with the suggested origin of post-necrotic scarring from a previous massive necrosis, would appear to justify the recognition of this group and its separation from the group of cases of cirrhosis giving rise to a diffuse hepatic fibrosis.

The incidence of post-necrotic scarring in this series - 8 cases out of 44 (18 per cent.) is higher than that (6-9 per cent.) reported by Karsner (1943) in a much larger series of cases. Some of this difference can be explained by the fact that three (Nos. 19, 41 and 42) of the cases are from a selected group of young patients operated on by Professor Sir James Learmonth because of recurrent haematemesis.

(3) Infective Hepatitis

The two cases of "acute" cirrhosis (Nos. 4 and 29) possess so much in common both in their history and in their histological appearances that they can be separated from the other cases and comment made on them.

It /

It could be questioned whether these cases should be included in this series at all, for the term cirrhosis suggests a picture of past hepatic damage with a nodular liver and reparative processes the main features, while in neither of these cases was the liver nodular, and apart from the presence of a marked excess of collagen, signs of repair were notably absent, the picture being one of active liver damage which has progressed over the period of a few weeks to death from liver failure. Both cases do, however, illustrate points of interest raised in Professor Himsworth's monograph, and serve to demonstrate the relationship between infective hepatitis and subsequent cirrhosis of the liver - a point over which there has been much discussion in recent years (Dible, McMichael and Sherlock, 1943; Howard and Watson (1947); Zimmerman and Thomas, 1948).

It has been recognised for several years now that the lesion produced by infective hepatitis is a zonal necrosis, the cells in the centre of the lobule becoming necrotic, but the reticulum framework remaining unaffected so that when the acute stage is past repair can occur and each lobule assume its normal form once more. It has been supposed that death occurred when a large enough part of each lobule was affected for hepatic insufficiency to ensue. Professor Himsworth suggests, however, that the eventual outcome of a case of infective hepatitis, as well as depending on the immediate virulence of the infection, is also conditioned by the state of nutrition of the patient at the time of infection, for infective hepatitis is recognised to possess a higher mortality in malnourished individuals (Hadfield and Garrod, 1947) and in pregnant women (Frerichs, 1860-61) /



1860-61) in whom essential nutriment may pass to the foetus at the expense of the maternal tissues.

In an extensive epidemic of infective hepatitis in Denmark, Havens (1946) reported an unusually high mortality amongst middle-aged women, either, it was thought, because of the presence of an excess of oestrogens in these women or to an excess of oestrogens administered therapeutically for menopausal symptoms.

Other recent work on the mortality rate in homologous serum jaundice, now considered to be due probably to the same virus as causes infective hepatitis, has served to emphasise further the relationship between the severity of the disease and the state of nutrition of the patient.

It has been noted already that in Professor Himsworth's view the patients who die following infective hepatitis are already in a subclinical state of protein deficiency which is unmasked by death of a proportion of liver cells and an acute massive necrosis of the liver supervenes. This theory gains considerable support from Lucke's work (1944 a and b) and from papers by Lucke and Mallory (1946), Mallory (1947) and Cullinan (1939), on the pathology of infective hepatitis, for they describe the changes seen at post mortem in fatal cases as being due to patchy areas of necrosis and haemorrhage along with other areas showing considerable regeneration of hepatic cells - the picture seen after Himsworth's acute massive necrosis.

The fact too that in both cases in this series there were at least two episodes of jaundice lends further support to the theory, for it will be remembered that one of the fundamental points /

points of importance in the production of acute massive necrosis was the occurrence of a latent period before the onset of the acute phase. This latent period was definitely present in Case No. 29, a case seen personally soon after admission to hospital, and the "recurring episodes of jaundice" referred to in the case history of the other case (No. 4) may have had a similar significance.

Though the pathological picture seen in the two cases under discussion is that recognised as typical of fatal cases of infective hepatitis (Mallory, 1947), the question as to whether antecedent infective hepatitis may cause subsequent cirrhosis would appear in these particular cases to be answered in the negative, for like all the fatal cases quoted by Lucke (1944 a and b), the disease from the onset of the phase of acute massive necrosis ran a rapidly fatal course. There was no indication in these two cases or in any cited by Lucke that reparative processes could stem the course of the disease sufficiently to give time for a cirrhotic process of the nature of a post-necrotic scarring to develop. Lucke himself (1944) is of the opinion that infective hepatitis is not a cause of subsequent cirrhosis.

Weight is added to this view by the fact that in spite of the many large and often serious epidemics of infective hepatitis which have been reported, particularly during the recent war, there has never been any corresponding rise in the incidence of cirrhosis of the liver: in fact the opposite opinion is held by Lucke (1944 a) who considered that after the 1914-1918 war when there was a sharp rise in the incidence of infective hepatitis the /

the incidence of cirrhosis of the liver had in fact fallen.

The other point of view has been put forward by Howard and Watson (1947) who found a history of previous infective hepatitis in a significantly higher percentage (33 per cent.) of patients with cirrhosis of the liver than in a control group of 100 cases in which the incidence of previous infective hepatitis was 7 per cent.

More recently still, Sherlock (1948) has followed up by serial liver biopsy nine cases of infective hepatitis (including three cases of homologous serum jaundice) who had been considered to have subsequently developed cirrhosis of the liver. In all these cases liver biopsy has shown the presence of a definite cirrhosis. In all the cases where biopsy of the acute stage was available, the illustrations demonstrate areas of necrosis with derangement of lobular architecture. Whether they were definite cases of infective hepatitis it is not so easy to say, for in some of them the primary episode of jaundice had occurred some time before they were first seen by the author.

A further comment will be made later in this part (Section 6) on the part played by infective hepatitis in relation to cirrhosis, but meanwhile it can only be concluded from a consideration of Cases Nos. 4 and 29 that they support Professor Himsworth's views on the etiology of human cirrhosis, and that the pathological picture seen in them is that seen in fatal cases of infective hepatitis. In neither case was there any ground to suppose that they might have progressed to produce cirrhosis of the liver.

(4) Cardiac Cirrhosis

At the beginning of this investigation cardiac cirrhosis was considered to be of rare occurrence and to be present only in a few cases of very long standing chronic venous congestion - usually in cases of constrictive pericarditis or in double valvular lesions. According to Koletsky and Barnebee (1944) cases should not be accepted as cases of cardiac cirrhosis unless in addition to some fibrosis there is also distortion of lobular pattern. Using this criterion, they found its incidence in 4200 consecutive autopsies was 30 cases, including the following:

Mitral stenosis	- 5 cases
Combined valvular disease	- 9 cases
Chronic pericarditis	- 5 cases

They describe as the typical sequence of events the proliferation of fibrous tissue around portal tracts and central veins, the proliferation being sometimes more prominent in one area and sometimes more prominent in another, but always in the fully developed case accompanied by slight lobular derangement though the arrangement of the cells in columns is usually preserved.

During the detailed examination of the material which forms this series, it was early realised that a group of cases showing minor degrees of cirrhotic change was emerging. In all these cases there was a very slight fibrosis and reaction around the portal tracts; the portal tracts tended to be clumped together in small groups, and associated with this clumping of the portal tracts there was definite, and, as far as could be judged from the /

the examination of the sections, well-marked distortion of the normal lobular architecture, so that the central veins did not retain their usual relationship to portal tracts. The columns of liver cells showed varying degrees of cellular activity (Fig. 3) and the sinuses were often conspicuously widened.

In two cases (Nos. 22 and 27) this appearance was associated with very long-standing cardiac failure, and in another case (No. 14) the changes of chronic venous congestion were seen in the right lobe while the left lobe showed all the changes described above with very well-marked nuclear activity (Figs. 1, 2 and 3). It was thereupon observed that in three other cases (Nos. 9, 10 and 34) occurring in elderly patients, and in one (No. 35) occurring in a younger man, there was also a possible history of long-standing "occult" chronic venous congestion. From these findings it would appear justifiable to associate these architectural changes with chronic congestive changes in the liver. Though in none of them is fibrosis a feature, they all otherwise fit in with the description given by Koletsky and Barnebee of cardiac cirrhosis.

These findings, on theoretical grounds, are not altogether surprising, for if cirrhosis is caused by lack of some nutriment in the blood, this state of affairs could also be reproduced in a person in whom nutriment is present in normal amount but in whom the blood supply to the liver is diminished by the presence of cardiac failure.

In Case No. 7 there is a history of long-standing and recurring cardiac failure with the changes of cardiac cirrhosis as described above present in both sections (one from the right lobe /

FIGURE 1

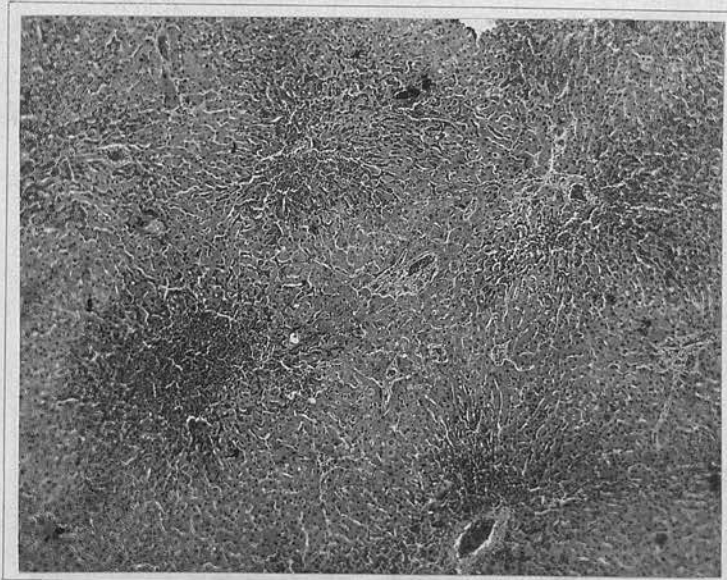


Figure 1 (X40) - Haematoxylin and Eosin (Case No. 14) from right lobe of liver: Note the well-marked lobular pattern accentuated by the presence of chronic venous congestion.

FIGURE 2

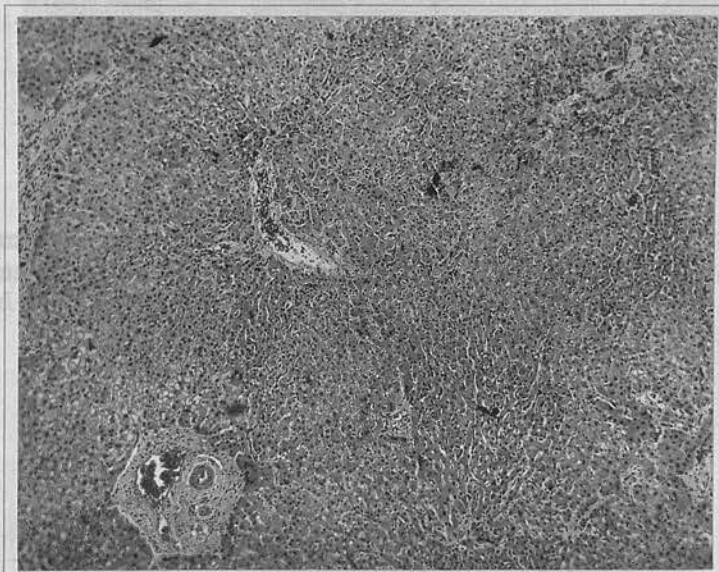


Figure 2 (X40) - Haematoxylin and Eosin (Case No. 14) from left lobe of liver: Here the lobular pattern is distorted and the one portal tract seen in the section is increased in size and shows some fibrosis and bile-duct proliferation.

lobe and one from the left). In the sections from the right lobe the appearances show a strikingly less marked distortion of the lobular architecture than from the naked-eye appearance.

FIGURE 3

therefore to theorise that the changes in the liver are due to a systemic disease though it appeared to be a local one.

basis of failure.

increasing

if this is

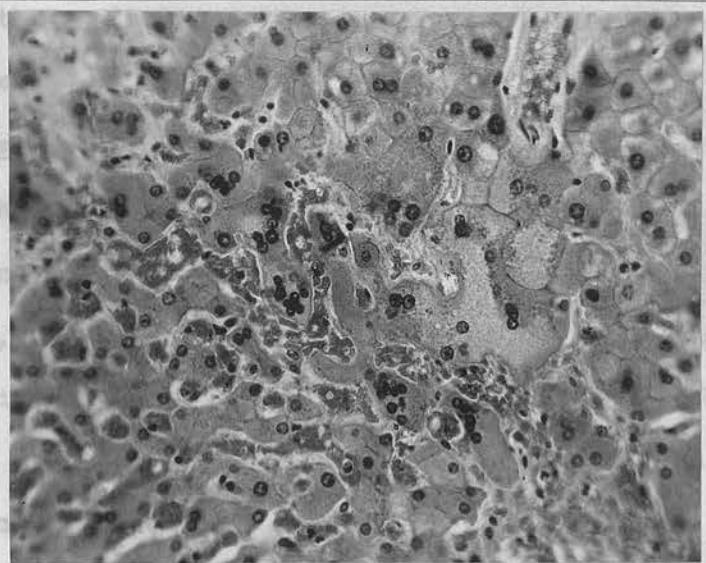
often found

after all,

be postulated

supply to

of certain



The jaundice associated with this condition is suggestive of cardiac failure may be due to a lack of liver cells which are anoxia, or, as is often the case, to a systemic disease.

Figure 3 (X300) - Haematoxylin and Eosin (Case No. 14):
High power view from the left lobe of the liver to show multi-nucleated liver cells.

state of knowledge as to the cause of these factors is responsible for the changes in the liver cells, but if they are due to lack of sufficient quantities of essential foodstuffs reaching these cells, this would be a local rather than a systemic disease. The distortion of lobular architecture which is seen in this condition is occurring on a similar basis to that which occurs in the liver in cases of cirrhosis. This point will be discussed in more detail in the next section.

On /

lobe and one from the left). In fact the microscopic appearances show a strikingly less marked degree of cirrhosis and distortion of the lobular architecture than would be expected from the naked-eye appearance of the organ. It is tempting therefore to theorise further and suggest that in this case, though it appeared to be one of post-necrotic scarring, the real basis of the condition has been repeated episodes of cardiac failure, each being recovered from and giving rise to increasingly severe cirrhosis. To meet the argument as to why, if this theory is correct, a markedly cirrhotic liver is not more often found in cases of recurrent cardiac failure, which is, after all, not such a very uncommon clinical condition, it must be postulated that as well as there being a deficient blood supply to the liver there must also be a deficiency in the blood of certain essential nutriment.

The jaundice associated with severe episodes of congestive cardiac failure may be due to death of liver cells either from anoxia, or, as is now suggested, death of liver cells due to lack of essential nutriment. It is not possible in our present state of knowledge to decide which of these factors is responsible for the changes in the liver cells, but if they are due to lack of sufficient quantities of essential foodstuffs reaching these cells, this would also explain the distortion of lobular architecture which occurs, the distortion occurring on a similar basis to that which occurs in more florid cases of cirrhosis. This point will be returned to again in Part V.

On /

On the experimental evidence of Bolton (1914), Zimmerman and Hillsman (1930) and Bolton and Barnard (1931), it was considered that cardiac cirrhosis when it occurred was a mechanical process due essentially to back pressure in the hepatic veins. Here, on the evidence of the cases quoted above, it is suggested that in some cases another factor is introduced by a deficiency in the forward circulation of blood in these cases.

(5) Cirrhosis without Fibrosis

Beattie and Dickson (1948) define cirrhosis of the liver as being a pathological process in which three main phenomena play a varying part:-

- (a) Overgrowth of fibrous tissue
- (b) Loss of some liver cell tissue
- (c) Hyperplasia of the remainder

It has already been noted in discussing cardiac cirrhosis that fibrosis may not be marked in some cases. Examination of the cases under review has shown that this is also true of other types of cirrhosis, for in three cases (Nos. 1, 2 and 13) cirrhosis of the liver was found to be present without any increase in the amount of fibrous tissue in the liver. In two of these cases (Nos. 2 and 13) the liver was coarsely nodular, the nodules being composed of small areas of hyperplastic liver cells and in only one case (No. 1), where the liver was not obviously nodular, was the correct diagnosis missed for some time, probably because the possibility of cirrhosis occurring without fibrosis was not appreciated. /

FIGURE 4



Figure 4: The liver from Case No. 2, showing the smoothly nodular surface.

FIGURE 5

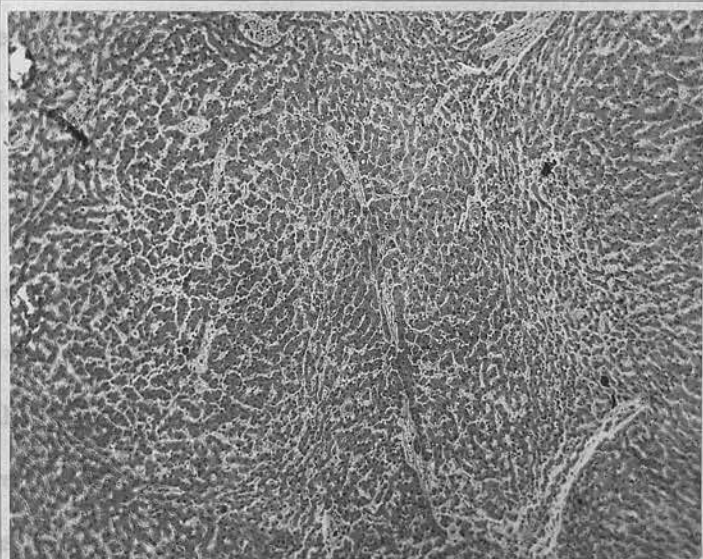


Figure 5 (X40) - Haematoxylin and Eosin. (Case No. 2): A typical field showing the marked disruption of the lobular architecture and the complete absence of new fibrous tissue - cirrhosis without fibrosis.

appreciated. In all three cases some of the usual complications of cirrhosis were present - ascites, splenomegaly and haematemesis - so that there can be little doubt that cirrhosis of the liver was present, death occurring in two cases (Nos. 2 and 13) from the liver condition.

At one time it was considered that many of the complications of cirrhosis of the liver were due to the contraction of the new fibrous tissue after it was formed. Doubt as to the validity of this belief was expressed by Kelly (1905) and these three cases provide still further argument against attaching too much importance to any possible influence the fibrous tissue may have on the course of the disease.

A fairly extensive survey of opinions which have appeared in the English and American literature on the pathology of cirrhosis of the liver during the past few decades has revealed no reference to such an entity as cirrhosis without fibrosis, though several papers have been published dealing with the possibility of repair and the reabsorption of the fibrous tissue which is present in cirrhosis of the liver. Though Henke and Lubarsch (1930) refer to the occurrence of "pseudo-cirrhosis" (cardiac cirrhosis) without fibrosis, no reference to the occurrence of true cirrhosis without fibrosis could be found.

In their much quoted paper on the induction of cirrhosis in rats by repeated small doses of carbon tetrachloride, Cameron and Karunaratne (1936) suggest that fibrous tissue once it is formed can be reabsorbed though a stage in the production of the cirrhosis is eventually reached when this can not take place.

Orr (1940) came to a similar conclusion after inducing cirrhosis of the liver, again in rats, by the administration of butter yellow and then allowing the lesion to heal. Here again the fibrosis disappeared. These experiments by Orr were repeated by Steinberg and Martin (1946) and still further controlled by the injection of thorium in order to prove by the presence of "ring shadows" in the liver that cirrhosis was indeed present. The cirrhosis was then allowed to heal and the disappearance of the fibrous tissue and ring shadows demonstrated. From this experimental work it would appear that fibrous tissue can in certain circumstances be reabsorbed.

Not all pathologists agree with this opinion (Sellars, 1946) and they consider that in some cases fibrosis is not definitely established but that condensation of the pre-existing reticulum, which is known to occur sometimes in these cases, has been mistaken for fibrosis. That condensation of reticulum does occur in some types of liver damage in man has been demonstrated by Dible, McMichael and Sherlock (1943).

There can be only two explanations to account for the absence of fibrosis in the three cases under discussion:-

- (1) Fibrous tissue had been present but it had been reabsorbed.
- (2) Fibrous tissue had never been present.

The first explanation has been shown to be at least a theoretical possibility, while there does not appear to be any obvious reason why the second explanation might not be valid also.

The /

The fibrosis which is found in a cirrhosis is usually thought to be either a type of replacement fibrosis or to be due to stimulation of fibroblastic activity by the same factor which caused the cirrhosis. It may be that some substances causing cirrhosis in man do not give rise to a fibrous tissue reaction or may be present in such small amount that there is stimulation of liver cell activity without either death of cells and the need for replacement fibrosis. That these patients are perfectly able to form fibrous tissue is shown by the occurrence of lienal fibrosis in all three cases.

Unfortunately there is no clue in any of the three cases as to etiology of the cirrhosis, except that in Case No. 13 there was a history of a few years' alcoholism before death. It is therefore not possible to tell what factors played a part in the production of the picture. The only point of interest common to all three cases is the size of the liver. In none of them is there a marked reduction in the size of the organ such as might be expected in a cirrhosis showing no fibrous tissue, for the fibrous tissue in a small cirrhotic liver must form a considerable portion of its weight. In this connection it is not improbable that the fibrous tissue is the cause of some of the ultimate decrease in size of these livers:-

Case No. 1 - 1320 g.

Case No. 2 - 1280 g.

Case No. 13 - 1160 g.

On the other hand, these weights are not obviously increased in amount, so that there has not been proliferation of liver cells without /

without at the same time death of other liver cells. It was realised by Mallory (1911) that in the group of cirrhosis he classified as toxic, the fibrosis was not due to the growth of new fibrous tissue but to collapse of small areas of liver tissue. In such cases therefore, if, due to a lack of patchiness in the distribution of the lesion, there was no collapse, there would be no fibrosis. In other words, the picture seen in these three cases would be produced.

After study of the cases, my own impression is that in these three there never has been any fibrosis and that in view of the facts put forward in the previous paragraph, and of lack of evidence to suggest any other mode of formation, these three cases should be regarded as cases of post-necrotic scarring.

(6) The Etiology of Human Cirrhosis

It will have been appreciated from the foregoing discussions that the more information about the previous mode of life, occupation, previous history and naked-eye description of the liver that is available, the more likely is it that more cases could be placed in their correct etiological group whether it be a group due to dietary, toxic or chemical factors, or a variable combination of these factors. In cases coming to post mortem, an adequate anatomical description of the organ is usually available, but unless a diagnosis of cirrhosis of the liver was made during life, and some very obvious factor was present as a likely cause of that condition, detailed information as to the dietary habits, previous history and contacts with possible /

possible toxins or chemicals, is not usually available.

It was therefore decided to interview personally as many patients as possible who had definite cirrhosis of the liver in order to ascertain in more detail what was the background to their clinical condition and in particular, in regard to Professor Himsworth's views, what part a possible dietary deficiency played in each case.

Unfortunately only 11 proved cases and one probable case (No. 48) of cirrhosis of the liver were available for examination during the period October 1948 to April 1949, so that while the findings are of interest, their significance is lessened by the small number of patients interviewed. As well as ascertaining their dietary background, an attempt was made to find out if the patients had, at any time, come into contact with hepatotoxic chemical substances, ever suffered from infectious hepatitis and also what part, if any, consumption of alcohol played in the production of their liver lesions.

The results of these enquiries in each individual case are given, then summarised in table form and discussed in some detail.

Male, age 44.

History

In the two years before his admission the patient had had four large haematomas followed in each case by ecchymoses and oedema. A liver-renal anastomosis was performed but he died four days later with a massive haematoma and portal vein thrombosis.

Previous History

The patient had malaria whilst serving in North Africa in 1945 in the R.E.F. but at no time had he ever been jaundiced. He had had no other illnesses.

Physical Examination

Case No. 19 (Professor Sir James Learmonth)

Male, aet. 24.

History:

About two years before admission the patient had two large haematemesis but after about six months, he was returned to full flying duties. Seven months before admission he had melaena and his spleen was noticed to be enlarged. Ten weeks before admission he had a further haematemesis. Lieno-renal anastomosis was performed, but the patient died four days later with a left haemothorax and haemoperitoneum.

Previous History

No illnesses of note and in particular, no history of jaundice.

Personal Habits

The patient had no marked food aversions and normally had a good appetite. He smoked 15 - 20 cigarettes a day and only drank a little, up until eighteen months before death, since when he had been teetotal.

Social History

He intended to enter the Civil Service on demobilisation from the R.A.F. where he performed flying duties. No history of contact with harmful chemicals was obtained.

Case No. 24 (Professor Sir James Learmonth)

Male, aet. 44.

History:

In the two years before his admission the patient had had four large haematemeses followed in each case by ascites and oedema. A Lieno-renal anastomosis was performed but he died four days later with a massive haematemesis and portal vein thrombosis.

Previous History

The patient had malaria whilst serving in North Africa in 1945 in the R.E.s. but at no time had he ever been jaundiced. He had had no other illnesses.

Personal Habits /

Personal Habits

The patient appeared to be in the habit of taking a good diet. He was a moderate smoker. He drank only occasionally and never to excess.

Social History

For many years the patient worked in quarries and part of his job lead to frequent contact with gelignite. During the war (1939 - 1945) he was first of all in the R.E.S. and later an Admiralty Civilian. Latterly he had been a public works contractor.

Case No.29 (Dr W.D.D. Small)

Female, aet. 54.

History:

The patient had been in contact with a case of infective hepatitis about three weeks before the onset of a fairly definite attack of infective hepatitis. The jaundice cleared a little but recurred and gradually became deeper till she died two months later of liver failure.

Previous History

Apart from influenza, she had had no illnesses of note and had never previously been jaundiced.

Personal Habits

Although "not a large eater" she had always appeared to have a good dietary intake. She did not drink or smoke.

Social History

The patient was not married and stayed by herself, but a sister and her daughter occupied rooms in her flat. She went out to work as a morning "help".

Case No. 40 (Mr T.MCW. Millar)

Female, aet. 64.

History:

The /

The patient had been feeling "off colour" and losing some weight for about two years. A few months before admission she became jaundiced and then her ankles and abdomen began to swell. Laparotomy was performed and a hard nodular liver found. The jaundice became less. The patient improved and was discharged home.

Previous History

Apart from childhood illnesses the patient had had no previous illnesses of note and in particular had never previously been jaundiced.

Personal Habits

Apart from finding that fats did not agree with her she appeared to have no dietetic difficulties and normally to eat a good diet. She did not smoke nor drink.

Social History

The patient is a housekeeper and has done only housework all her life, having had no known contacts with chemicals.

Case No. 41 (Professor Sir James Learmonth)

Male, aet. 38.

History:

The patient had a small haematemesis in 1941 and two months before his admission, a large haematemesis. Splenectomy was performed but the patient died three weeks after operation with a portal vein thrombosis.

Previous History

The patient had had no previous illnesses and in particular he had never been jaundiced nor, so far as he was aware, had he been in contact with anyone suffering from infective hepatitis.

Personal Habits

He had no food fads and had always eaten a good mixed diet. He had been married for ten years. He was a heavy smoker but a moderate drinker, usually drinking beer.

Social History

For fifteen years after leaving school the patient was a chemist /

chemist, then was in the Army for two years before being transferred to a munition factory where he worked with pharmaceutical drugs and also handled benzene and trichlorethylene. Since the war he had been a publican. The contact with the hepatotoxic compounds was after his small haematemesis in 1941.

Case No. 42 (Professor Sir James Learmonth)

Male, aet. 27.

History:

During the six months prior to his admission, the patient had been becoming thinner and his abdomen distended. Splenectomy was performed and the patient is now convalescent.

Previous History

Apart from the usual childhood illnesses the patient has always been very healthy. He has never been jaundiced although he has been in contact with cases of infective hepatitis.

Personal Habits

He has no food fads and appears always to have had a good dietary intake. He smokes a good deal and until eighteen months ago, when he was married, he drank a good deal fairly regularly - three pints of beer a day, and five to six pints at the week-end.

Social History

After leaving school the patient did odd jobs, never associated with handling chemicals. During the periods 1938-1941 and 1946-1949 he worked in a brewery where he could have three pints of beer a day without payment. The beer, he affirms, definitely helped his appetite. From 1941-1946 he served with the Royal Marines in Europe and in Ceylon.

Case No. 43 (Professor Sir James Learmonth)

Male, aet. 20.

History /

History:

During the seven months before admission, the patient had had three large haematemeses. A Lieno-renal anastomosis was performed and the patient remains well, two-and-a-half months later.

Previous History

Although the patient described himself as having had a "bit of a paunch" for three years, he has otherwise always considered himself to be very healthy, apart from an operation for a hernia in 1939. He has never had jaundice although, in hospital in West Africa, he came into contact with some patients who had infective hepatitis.

Personal Habits

His food intake has always been good and apart from a dislike for cheese, he has no fads. Until a few months ago his appetite had always been good.

Social History

After leaving school the patient was apprenticed as a motor-mechanic. In 1947 he was called up and was drafted to West Africa as a motor-driver. He had, on occasions, used carbon tetrachloride to take grease stains out of his clothes and while in the Army he occasionally worked, with due precautions, with a vat of the same substance.

Case No. 44 (Professor Sir James Learmonth)

Male, aet. 26.

History:

The patient has had four very small haematemeses during the past four years. Splenectomy was performed a few weeks ago and the patient has remained well since.

Previous History

The patient has never had a day's illness in his life, so far as he is aware, and in particular, he has never been jaundiced.

Personal Habits /

Personal Habits Case No. 45 (Professor D.M. Iyem)

He has always a good appetite, living and working on a farm, with three cooked meals a day. He smokes two to three cigarettes a day and is teetotal.

Social History

Since leaving school the patient has worked on his father's farm. He was not called up to the Armed Forces and apart from his work with a tractor and agricultural fertilisers, he has had no known chemical contacts.

Previous History

Case No. 45 (Dr W.A. Alexander) He has never been jaundiced.

Female, aet. 60.

History:

The patient had been feeling increasingly weak and unwell for about two years before admission. About a year before admission, and again about six months later, she had a large haematemesis.

Previous History

For about ten years now the patient has complained of a dull ache in her left side (? enlarged spleen), but apart from this and the facts noted above, she has had no illnesses of note. She has never been jaundiced.

Personal Habits

She said she was brought up strictly and has no food fads but she does appear to be the type of woman who would be fussy about her food. She does not smoke and only has an occasional drink on anniversaries.

Social History

For six to seven years after leaving school she worked on a loom in a tweed mill. She was then married, and since has done only housework. She has never worked with chemicals.

Case /

Case No. 46 (Professor D.M. Lyon)

Apart from pneumonia in 1945, she has had no illness of
Male, aet. 67.

History:

For three months before admission, the patient had been losing weight and his abdomen becoming swollen. His liver was palpable four fingers breadth below the costal margin. Biochemical tests showed evidence of impaired liver function. No lesions were detected in his gastrointestinal tract. Clinically he was probably a case of cirrhosis of the liver.

Previous History

He can remember no previous illnesses. He has never been jaundiced.

Personal Habits

His dietary habits are very poor as he lives by himself and has been a widower for seventeen years. He very rarely has a cooked meal. He smokes twenty cigarettes a day and drinks a good deal at week-ends.

Social History

After leaving school he spent seven years as an engineering apprentice; was in the Army from 1914-1918; served at sea for ten years and since then, has worked as a pithead engineman. Apart from oils and cleaning materials he has had no contact with possible injurious chemicals.

P.M. 26. 4.49

The liver was coarsely nodular and contained many small tumour nodules scattered throughout, the appearances being those of multiple hepatomas in an otherwise cirrhotic liver.

Case No. 47 (Dr R.W.D. Turner)

Female, aet. 45.

History:

The patient complained, about May 1944, of swelling of her abdomen. Omentopexy was performed but regular tapping has been required since. At operation the liver was noted to be grossly cirrhotic.

Previous History /

Previous History

Apart from pneumonia in 1946, she has had no illness of note and has never been jaundiced.

Personal Habits

Since she was twenty years old the patient has drunk a very great deal, mainly spirits, but when unobtainable, she drank methylated spirit. This was so for six years. Her dietary intake, largely because of her financial condition and her drinking, has been poor for years.

Social History

The patient worked in a rubber mill making bicycle tyres for four years after leaving school. Since then she has worked at home. At no time has she had contact with injurious chemicals.

Case No. 48 (Dr R.W.D. Turner)

Male, aet. 63.

History:

The patient was admitted one year ago with bilateral apical pneumonia and at that time his liver was noted to be enlarged. On questioning he was found to have had some breathlessness on exertion and occasional oedema of the ankles for five years. No evidence has been found to suggest this is not a case of cirrhosis of the liver.

Previous History

After the 1914-1918 war, the patient had "trench foot". He had pleurisy at the age of eighteen and pneumonia six years ago. He has never been jaundiced, but in 1914, a friend had jaundice.

Personal Habits

For many years the patient carried a "piece" to his work but had a cooked meal on his return home. He has always had a good appetite and has no food fads. Until six years ago he had been a heavy cigarette smoker but since then, he has not smoked. Up to one year ago he had taken his four pints of beer at the brewery and had drunk more beer and spirits at the week-end.

Social Habits

After /

(a) After leaving school, at the age of eleven, the patient worked with a butcher for three years, then with an iron-monger for six months, before starting as a cooper in a brewery. At no time has he ever worked with injurious chemicals.

deficient in protein. In both these cases this is associated with an excessive intake of alcohol, gross in one and moderate

Summary of Findings

in the other, but in both, the two factors taken together appear

sufficient, when based on TABLE IV Himsworth's work, to give

rise to diffuse hepatic cirrhosis and all the sequelae thereof.

Case No.	Sex	Age	Diet		Alcohol	Chemicals	Infective Hepatitis
			Good	Poor			
19	M	26	+++	-	-	-	-
24	M	44	++	-	-	?+	-
29	F	54	++	-	-	-	+
40	F	64	++	-	-	-	?+
41	M	38	++	-	+	?+	-
42	M	27	++	-	++	-	-
43	M	20	++	-	-	?+	-
44	M	26	+++	-	-	-	-
45	F	60	+	-	-	-	-
46	M	67	-	+++	++	-	-
47	F	45	-	+++	+++	+	-
48	M	63	+++	-	++	-	-

The whole of this argument is invalidated by the fact that

The various factors responsible for the production of the

liver lesions in these cases will be considered in more

detail.

would seem, therefore, that the alcoholic intake, which should

(a) Diet /

(a) Diet

In two of the cases (Nos. 46 and 47), there was a very definite history of a deficient food intake, especially deficient in protein. In both these cases this is associated with an excessive intake of alcohol, gross in one and moderate in the other, but in both, the two factors taken together appear sufficient, when based on Professor Himsworth's work, to give rise to diffuse hepatic cirrhosis and all the sequelae thereof. It is unfortunate that no biopsy specimens are available in either of these cases to verify the diagnosis or indicate the histological appearance of such a condition in man. The rôle of alcoholism and a lack of lipotropic substances in the blood in the production of cirrhosis of the liver has already been discussed and these two cases quoted above serve to underline the association. The importance of this association is slightly offset by the findings in Cases No. 42 and 48 where the patients affirmed that the intake of 3-4 pints of beer a day at their work did not affect their appetites and in fact served to sharpen them. As this fairly large consumption of alcohol did not seem to be in any way associated with a poor food intake it can only be assumed that the regular consumption of such large amounts of beer each day interfered in some way with the absorption of the rest of the food from the intestine.

The whole of this argument is invalidated by the fact that pathological examination has revealed that the cirrhosis in Case No. 42 appears to be due to post-necrotic scarring. It would seem, therefore, that the alcoholic intake, which should in /

in theory have produced the picture of a diffuse hepatic fibrosis, has in this case done no more than perhaps accelerate a process based on some other unknown etiological factor.

(b) Alcohol

This factor has been fully dealt with in the discussion on diet.

(c) Chemicals

Although a history of contact with injurious chemical substances was obtained in four cases (Nos. 24, 41, 43 and 47), it is doubtful how much emphasis should be placed on these findings. In two of them - the handling of gelignite (No. 24) and the occasional use and exposure to the fumes of carbon-tetrachloride (No. 43) - the significance of the chemical contact is especially doubtful. The fact that the exposure to benzene and trichlorethylene was subsequent to the first haematemesis would also seem to lessen the importance which would otherwise be attached to these contacts in Case No. 41. The fourth and remaining case was addicted to the drinking of methylated spirit, a factor which would almost certainly, in association with her alcoholism mitigate still further against a sufficient food intake.

It can be concluded therefore that though chemical contacts were present in these cases, the part, if any, which they played in the production of the cirrhosis can not be determined.

However, /

However, in the absence of other possible etiological factors in three of these cases (Nos. 24, 41 and 43), it must be accepted that as the chemical substances involved are known to be capable of producing hepatic damage, their association with these cases cannot but be regarded as significant.

(d) Infective Hepatitis

The only case in this series which, in spite of careful questioning, often with the putting of leading questions, gave a history of previous infective hepatitis was Case No. 29 and here, as has already been discussed in a previous section, the infective hepatitis set in action a rapidly fatal chain of events. Attention has also been drawn to the fact that it is doubtful if this case should be regarded as a case of cirrhosis of the liver, but as Cullinan (1939) has pointed out, there is a picture of subacute yellow atrophy of the liver in fatal cases of infective hepatitis and this picture would appear to be the same as in Professor Himsworth's acute massive necrosis.

symptoms from the carcinoma, reported as being perfectly healthy.

The important lesson therefore, to be learned from this small group of cases is that though cirrhosis of the liver in man may be due to a deficiency of choline, methionine or cystine, the factors which condition this deficiency are not yet understood. It would appear that as there is no obvious deficiency in the dietary intake, there must be some breakdown either in the absorption or utilization of the choline, methionine or cystine present in that diet.

Though /

DISCUSSION

It will be seen that in these twelve cases a possible etiological factor was found in six cases (Nos. 24, 29, 42, 46, 47 and 48) and in a further two (Nos. 41 and 43) though the basic cause was not found, further factors adversely influencing the progress of the disease were present. It has been already emphasised that though these etiological factors were present, it is by no means certain that they gave rise to the cirrhosis which was also present, so that it is probably of more value and more instructive to regard the results obtained from the opposite viewpoint - that is, that in six cases (50 per cent) no definite etiological factor could be found and, even if the two cases in which secondary damage may have been present (Nos. 41 and 43) and Case No. 45 in which the dietetic history was thought to be a little unreliable are omitted, three cases (Nos. 19, 40 (? infective hepatitis) and 44) remain, in which there is no clue as to why cirrhosis of the liver should have developed. All three patients were, up to appearance of their first symptoms from the cirrhosis, regarded as being perfectly healthy.

The important lesson therefore, to be learned from this small group of cases is that though cirrhosis of the liver in man may be due to a deficiency of choline, methionine or cystine, the factors which condition this deficiency are not yet understood. It would appear that as there is no obvious deficiency in the dietary intake, there must be some breakdown either in the absorption or utilisation of the choline, methionine or cystine present in that diet.

Though /

CONCLUSIONS

Though they are not points brought out by this series of cases, it does seem possible that, as well as there being a deficiency of certain factors in the diet, in some cases the onset of the cirrhotic process may be expedited by the hereditary background of the patient (King, Parsons, Penny and Freeman, 1948) or by his allergic pattern (Jaffre 1944) so that cirrhosis may be more liable to develop in some livers than in others.

- (1) 11 cases of diffuse hepatic fibrosis (on naked-eye appearance)
- (2) 3 cases of post-neurotic scarring (cirrhosis without fibrosis)
- (3) 2 fatal cases of infective hepatitis
- (4) 7 cases of "cardiac" cirrhosis.

Study of the case material would therefore indicate that a proportion of cases of cirrhosis of the liver in man can be classified either as being due to diffuse hepatic fibrosis or post-neurotic scarring, thus tending to support the theories of the development of cirrhosis of the liver propounded in Professor Rimmow's monograph. The factors which condition the production of cirrhosis of the liver are not yet properly understood in man.

Cardiac cirrhosis is a more common entity than is realized, mainly because its possible occurrence without fibrosis has not been appreciated. The possible pathogenesis of this type of cirrhosis has been discussed and it has been pointed out that as well as an increase in pressure in the hepatic veins of these cases, there is also a deficiency of blood /

CONCLUSIONS

Using the criteria laid down in the introduction to this chapter, study of 44 cases of cirrhosis of the liver has shown that:

- (1) 3 cases could be labelled "diffuse hepatic fibrosis"
 - (2) 8 cases could be labelled "post-necrotic scarring"
- and after discussion of the remainder, to these can be added
- (3) 11 cases of diffuse hepatic fibrosis (on naked-eye appearance)
 - (4) 3 cases of post-necrotic scarring (cirrhosis without fibrosis)
 - (5) 2 fatal cases of infective hepatitis
 - (6) 7 cases of "cardiac" cirrhosis.

Study of the case material would therefore indicate that a proportion of cases of cirrhosis of the liver in man can be classified either as being due to diffuse hepatic fibrosis or post-necrotic scarring, thus tending to support the theories of the development of cirrhosis of the liver propounded in Professor Himsworth's monograph. The factors which condition the production of cirrhosis of the liver are not yet however understood in man.

Cardiac cirrhosis is a more common entity than is realised, mainly because its possible occurrence without fibrosis has not been appreciated. The possible pathogenesis of this type of cirrhosis has been discussed and it has been pointed out that as well as an increase in pressure in the hepatic veins of these cases, there is also a deficiency of blood /

blood and therefore of nutriments.

Cirrhosis, without fibrosis, has been shown to occur in three cases and the factors leading to its production have been discussed. No reference to such an entity has been found in the British or American literature consulted.

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PART II

THE PORTAL AND SPLENIC VEINS

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INTRODUCTION

The association of cirrhosis of the liver, phleboscлерosis of the portal and splenic veins and splenomegaly was noted by Banti (1898), who considered that the primary pathological process occurred in the spleen and that the spread of some toxic substance along the splenic and portal veins to the liver was the cause of the changes found in these vessels and in the liver. However, the fact that the mesenteric veins usually show changes similar to those present in the portal and splenic veins, indicate that this explanation was incorrect (Epplen 1922). No case has been demonstrated in which the typical changes described by Banti were present in the spleen without accompanying liver disease (McMichael 1934) or obstruction in the splenic or portal veins (Kelsey et al 1947). In all these cases there is either intrahepatic obstruction to the venous return from the spleen or extrahepatic obstruction in the splenic or portal vein (Thomson 1940). The term 'Banti's Disease' has therefore been dropped and the term 'The Banti Syndrome' is used to describe cases in which there is obstruction to the venous outflow from the spleen and which show splenomegaly as their most marked clinical feature. McMichael (1932) thought that some cases of the Banti Syndrome could not be explained in this way and that the pressure in the portal vein depended to some extent on the pressure in the mesenteric artery.

For many years following the publication of Banti's original paper controversy over the relationship of the cirrhosis of /

of the liver and the changes in the spleen continued, but it was not until Simmonds (1912) again pointed out that changes did occur in the portal and splenic veins in cirrhosis of the liver and the Banti Syndrome that the relationship between the changes in these veins to pathological conditions in the liver and spleen, was again emphasised. McMichael (1934), in his paper on hepato-lienal fibrosis commented on the changes in the veins, describing them as hypertrophy of the muscle-coats with intimal fibrosis. It was not, however, until recently that these changes were examined in more detail (Pei-Lin 1940).

In his paper Pei-Lin compares and contrasts the changes produced by an increase in pressure in the portal and splenic veins with those found in the inferior vena cava when there is increased venous pressure in it. He found that the main change present under conditions of increased venous pressure was muscular hypertrophy of both sets of veins, the hypertrophy being more marked in the medial muscle of the portal vein and splenic vein and in the adventitial muscle of the inferior vena cava.

He also pointed out that in the portal and splenic veins hypertrophy of the muscle layers is often succeeded by intimal changes, small muscle bundles arranged longitudinally arising in the intima as a response to increased pressure in the lumen. According to Pei-Lin it is replacement of these muscles by fibrous tissue which produces the thickened fibrosed intima present in some cases. It was noted that degenerative and atheromatous changes were not seen to occur.

Stimulated /

Stimulated by Pei-Lin's paper which forms the basis of this chapter and in the hope that examination of the portal and splenic veins would give a reasonably accurate and measurable index of the degree of portal hypertension present in each case, the portal and splenic veins of 38 cases of cirrhosis of the liver and the Banti Syndrome were examined and the findings noted.

So far as possible, sections of the portal vein were taken from a point midway between its origin and bifurcation into its two main branches. Sections of splenic veins were taken from the vessel in its course along the posterior aspect of the pancreas. Transverse sections of these veins were stained with

- (1) Haematoxylin (Meyer's) and Eosin.
- (2) Weigert's elastic tissue stain counterstained with van Gieson's connective tissue stain.
- (3) Heidenhain's Azan stain.

Examination of the three different slides gave a good composite picture of the pathological changes present. The sections stained for elastic tissue, as well as showing up any change in the amount of elastic tissue, served to show up clearly the extent of any intimal thickening, for the stain brought out the internal elastic lamina and this structure was taken as the line of demarcation between the intima and the media. The section stained Azan made any increase in the size of the muscle-coats stand out clearly by differentiating the muscle from surrounding fibrous tissue.

Study of sections from the splenic veins found a useful means /

means of further determining the sequence of events in the portal vein in response to increase of pressure, for, as Pei-Lin showed, the changes found in the splenic vein were less pronounced than in the portal vein of the same case.

Since some of the material examined was obtained by biopsy the only portion of the splenic vein available in these cases was from the terminal centimeter of the vein as it entered the spleen. It is noted that the portal vein is also available for study in this case.

In addition to these cases, a case of Budd's Syndrome was examined in which the increase in venous pressure was due to the presence of an angiotoma of the portal vein. Sections were obtained from the portal vein and the angiotoma and the findings in this case assist the study of the sequence of events which take place in the portal and splenic veins as a response to increased pressure.

The histology of the portal vein in 28 normal control cases is described by Pei-Lin, this description coinciding with that of the normal histology of the portal vein as described by Maximow and Bloom (1948) and Cunningham (1939). Sections were examined from three control cases, (Nos. 49, 50 and 51).

Case No. 42 /

THE CASE MATERIAL

Sections from the portal, and occasionally from the splenic veins were available in 31 cases of cirrhosis while small portions of the splenic vein were obtained from 7 cases in which splenectomy was performed because of recurring haematemesis or splenomegaly. One of these cases (No. 13) later came to post mortem so that the portal vein is also available for study in this case.

In addition to these cases, a case of Banti's Syndrome was examined in which the increase in venous pressure was due to the presence of an angioma of the portal vein. Sections were obtained from the portal vein and the angioma and the findings in this case assist the study of the sequence of events which take place in the portal and splenic veins as a response to increased pressure.

The histology of the portal vein in 28 normal control cases is described by Pei-Lin, this description coinciding with that of the normal histology of the portal vein as described by Maximow and Bloom (1948) and Cunningham (1939). Sections were examined from three control cases, (Nos. 49, 50 and 51).

Case No. 49 /

Case No. 49

225/48. Male, aet. 38.

History:

The patient died following perforation of a duodenal ulcer.

Liver

Was normal and the spleen showed only a slight 'septic' reaction.

Case No. 50

268/48. Female, aet. 20.

History:

The patient had been ill with miliary tuberculosis for about six weeks before her death. Despite treatment with streptomycin she died of tuberculous meningitis.

Liver

The liver and spleen showed no obvious abnormality apart from the presence of numerous small healed tubercles on both organs. There was no upset of the lobular architecture of the liver.

Case No. 51

266/48. Female, aet. 44.

History:

The patient had a colostomy established because of diverticulitis. The colostomy was closed but the patient died a few days later with an acute diffuse generalised peritonitis.

Liver

Showed well-marked fatty changes in the cells of the central two-thirds of the lobules but no upset of the lobular architecture. The spleen, apart from an early 'septic' reaction /

reaction, was normal.

In the first two cases the histological appearance of the vein was similar to that described by the authors already quoted. The third case (No. 51) showed minimal intimal thickening of the wall of the portal vein and as the liver in this case could not be said to be normal, it was felt that the slight changes in the vein wall might have been secondary to the changes in the liver.

Only cases Nos. 49 and 50 were therefore taken as controls showing the normal structure of the portal vein and to them were added two cases (Nos. 9 and 10) from the series of veins studied, which showed no pathological changes in their walls.

Pei-Lin found that the normal structure of the splenic vein was similar to that of the portal vein except that the adventitial muscle was less prominent and more loosely arranged. That this was the case was verified in one normal control and in three other cases (Nos. 10, 14 and 51).

In view of the uniformity of the descriptions of the normal appearance of the portal and splenic veins verified in the few cases examined personally, further control cases were not investigated.

Preliminary study of the cases revealed that the changes in the veins brought about by an increase of pressure in them, could be graded, and to avoid unnecessary repetition of description /

description, these changes were classified into four main groups and a typical case from each group described in detail. Many individual variations were seen in the structure of the vein walls and uniformity within each group was not complete. A table was therefore compiled giving the main findings in each individual case.

The case material was divided into groups showing:-

1. A normal appearance of the portal vein.
2. Slight hypertrophy of the muscular and the medial elastic tissue with minimal intimal changes.
3. More marked hypertrophy of the muscular coats with definite, usually diffuse, intimal thickening.
4. The superimposition on the changes in the previous group of well-marked intimal thrombosis.

The description of the case material consists therefore of a detailed account of the histological findings in a typical case from each group followed by a résumé in table form of the findings in all the cases studied.

Case notes of four cases which have not been previously met with in this study are given and the findings in Case No. 55 described in some detail.

GROUP I /

GROUP I

A normal portal vein (Figs. 6 and 7).

Case No. 49

The endothelium lining the vein was not clearly seen but it appeared to be directly applied onto the innermost layer of the medial elastic tissue no subendothelial layer being visible. The elastic tissue of the media ran between the muscle cells in a longitudinal direction in long, thin, wavy strands, the innermost strand being the thickest and best-defined and forming the internal elastic lamina.

Also present in the media there was a compact layer of circular muscle fibres 2-4 cells thick, separated by a few loose strands of connective tissue. External to the media and separated from it by a few more connective tissue cells was a loosely formed adventitia composed of 2-3 small bundles of longitudinally-arranged muscle cells. Between these muscle bundles ran loose connective tissue and a few scattered elastic tissue fibres running mainly in a longitudinal direction.

External to this again there was more loose connective tissue in which ran nerve bundles and blood vessels.

Figure 7 (X220) - Weigert and van Gieson - Group I:
A normal portal vein (Case No. 49).

FIGURE 6

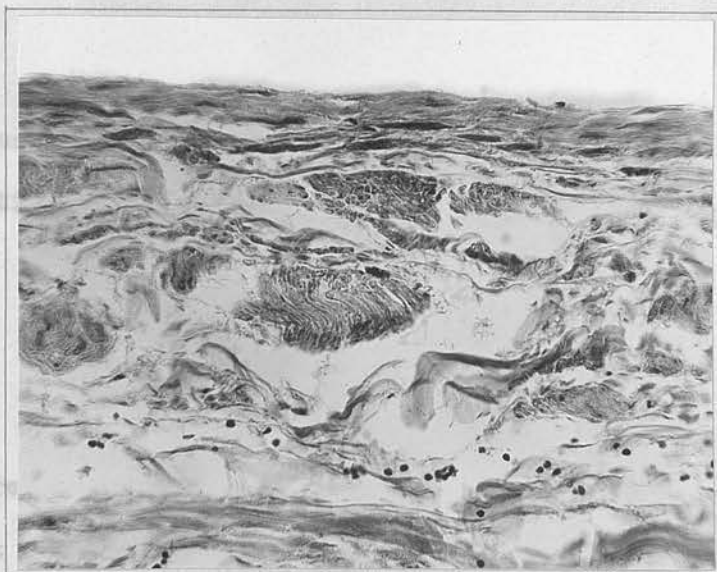


Figure 6 (X220) - Azan.

FIGURE 7



Figure 7 (X220) - Weigert and van Gieson - Group I:
A normal portal vein (Case No. 49).

GROUP II

Cases showing slight hypertrophy of the muscular and elastic tissue coats with minimal intimal changes (Figs. 8 and 9).

Case No. 22

There was an increase in the thickness of the vein wall due to slight hypertrophy of all its coats. Although some portions of the vein wall showed no intimal thickening, in other parts there was slight patchy intimal thickening due to the development in the subendothelial layer of small muscle cells cut transversely and occurring in small groups around which were one or two thin strands of elastic tissue.

The internal elastic lamina was slightly thickened and stood out more clearly than in the normal vein while the elastic tissue fibres present in the media were also increased in size and prominent. They did not appear to be increased in number. Both the medial and adventitial muscle cells were slightly increased in size.

FIGURE 8

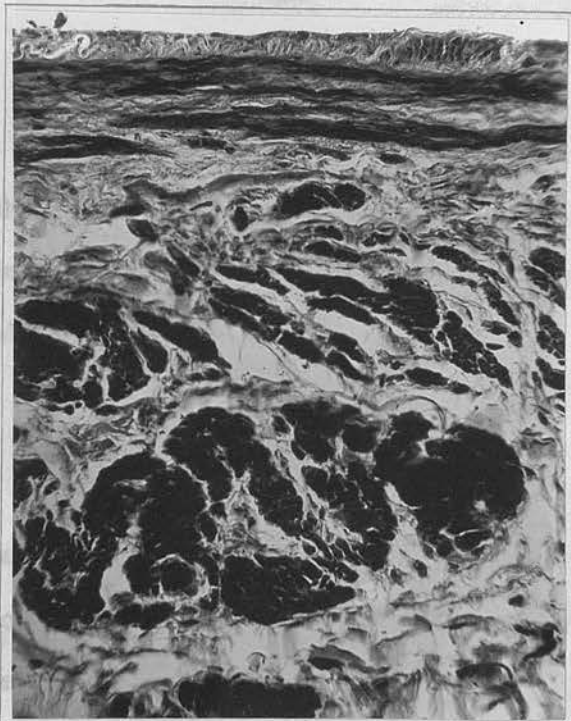


Figure 8 (X220) - Azan.

FIGURE 9



Figure 9 (X220) - Weigert and van Gieson - Group II:
Showing slight hypertrophy of the (Case No. 22) muscular and elastic tissue coats of the portal vein with minimal intimal changes. As the magnification is the same as that used in the illustrations of the normal portal vein, the hypertrophy of the muscular coats present in Figures 8 and 9 is well brought out.

GROUP III

Cases showing more marked hypertrophy of the muscular coats with definite, usually diffuse intimal thickening (Figs. 10 and 11).

Case No. 25

Here the vein wall was definitely thickened due to changes in all the coats. The intima was diffusely thickened and through it were scattered small muscle cells, usually cut transversely, around which ran many small, thin fibres of elastic tissue mainly circular in direction. Through the intima ran many thin, collagenous strands. The most superficial portion of the intima was a homogeneous, pale colour, and in the lumen of the vein, small numbers of red blood-corpuscles were observed adherent to the vein wall, sometimes, it was thought, with a covering of endothelium over them.

The internal elastic lamina was prominent and throughout the media were very numerous, short, thick, elastic tissue fibres, cut both longitudinally and transversely. The medial muscles as well as showing slight hypertrophy, were also increased in number so that the media was now 6-8 muscle cells thick.

The adventitial muscles were also slightly hypertrophied and the muscle bundles were larger and more closely arranged than in the normal vessel. Though there was no increase in the number of muscle bundles in the adventitia, the muscle cells were increased both in number and in size. There was no obvious increase in the amount of elastic tissue in the adventitia.

FIGURE 10

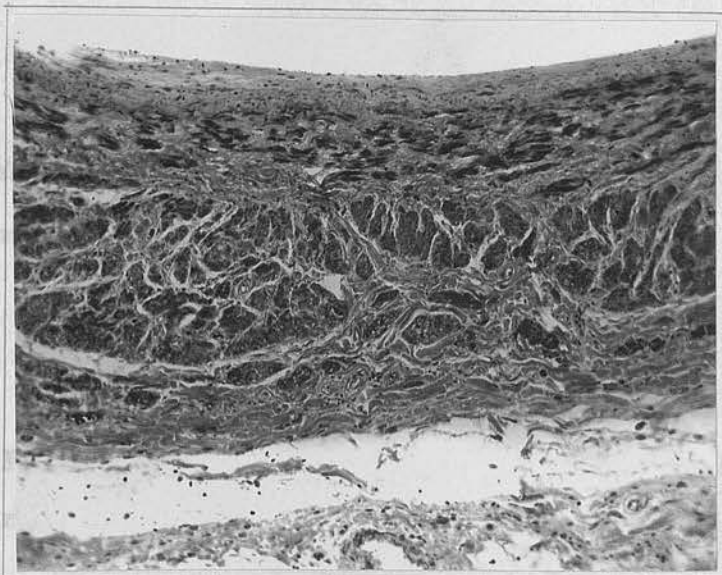


Figure 10 (X80) - Azan.

FIGURE 11

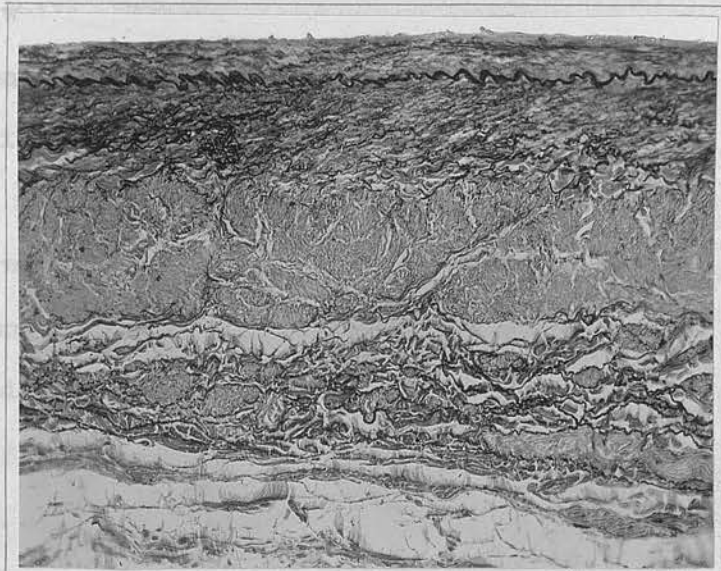


Figure 11 (X80) - Weigert and van Gieson - Group III:
Showing more marked hypertrophy of (Case No. 25) the muscular
coats of the portal vein with definite diffuse intimal
thickening.

GROUP IV

Cases showing well-marked thrombosis superimposed on the changes noted in the previous group (Figs. 12 and 13).

Case No. 2

The prominent feature in this section was the presence of a large, recently-formed thrombus on an already eccentrically thickened intima; eccentrically thickened, presumably because of previous thrombotic episodes, for it was composed of dense collagenous tissue and the recently formed thrombus was being invaded by active-looking fibroblasts. In the deeper portion of the thickened intima there were many well-formed vascular channels while, internal to this again, there was marked proliferation into the intima, of many small, elastic tissue fibres.

The internal elastic lamina was not easy to distinguish amongst a mass of elastic tissue fibres for the media was largely replaced by very marked proliferation of elastic tissue fibres, only a few scattered muscle cells remaining. External to the media the adventitia consisted of markedly hypertrophied bundles of longitudinal muscle cells, probably cut slightly obliquely.

As the edges of the eccentrically thickened intima were approached, the hypertrophy of the various layers became slightly less marked.

FIGURE 12

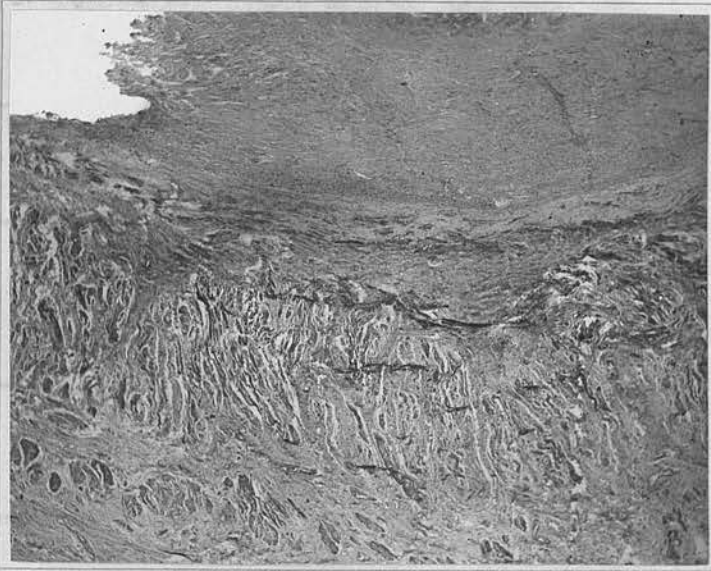


Figure 12 (X15) - Azan.

FIGURE 13



Figure 13 (X15) - Weigert and van Gieson - Group IV:
Showing well marked thrombosis (Case No. 2) superimposed on the
changes noted in Group III. Note the marked reduplication of
the elastic tissue in the media: it has replaced most of the
medial muscular tissue.

TABLE V - PORTAL AND SPLENIC VEINS

Case No.	Age	Adventitia		Media			Intima				Group
		Muscular Hypertrophy	Fibrosis	Muscular Hypertrophy	Fibrosis	Elastic Tissue	Muscles	Elastic Tissue	Fibrosis	Thrombosis	
1 S.V.	43	-	+	+++	-	+++	+	+	+	+++	IV
2 S.V.	49	+++	+	+++	-	+++	+	+	+	+++	IV
3	66	+++	+	+++	-	+++	+	+	+	+++	IV
4	34	+	-	+	-	+	+	+	+	+	III
5 S.V.	57	+	-	+	-	+	+	+	+	+	III
6	75	+	-	+	-	+	+	+	+	+	III
7	34	+	+	+	+	+	+	+	+	+	III
8	57	+	-	+	-	+	+	+	+	+	III
9	72	-	-	-	-	-	+	+	+	+	I
10 S.V.	75	-	-	-	-	-	+	+	+	+	I
11 S.V.	47	+	-	+	-	+	+	+	+	+	III
12 S.V.	77	+	-	+	-	+	+	+	+	+	III
13 S.V.	48	+	-	+	-	+	+	+	+	+	III
14 S.V.	72	-	-	-	-	-	+	+	+	+	I
15	29	-	-	-	-	-	+	+	+	+	III
16	19	-	+	+	+	+	+	+	+	+	III
17 S.V.	53	+	-	+	-	+	+	+	+	+	III
18	62	+	-	+	-	+	+	+	+	+	III
19	24	+	-	+	-	+	+	+	+	+	III
20	37	+	-	+	-	+	+	+	+	+	III
21	51	+	-	+	-	+	+	+	+	+	III
22 S.V.	63	+	-	+	-	+	+	+	+	+	III

TABLE V - PORTAL AND SPLENIC VEINS
(continued).

Case No.	Age	Adventitia		Media			Intima				Group
		Muscular Hypertrophy	Fibrosis	Muscular Hypertrophy	Fibrosis	Elastic Tissue	Muscles	Elastic Tissue	Fibrosis	Thrombosis	
23 S.V.	60	+	-	+	+	+	+	+	+	-	III
24 S.V.	44	++	+	++	+	++	+	++	+	++	III
25 S.V.	40	++	+	++	-	++	+	++	+	++	IV
26	64	+	-	+	-	+	+	+	+	+	III
27	54	+	-	+	-	+	+	+	+	+	III
28	39	+	-	+	-	+	+	+	+	+	III
29	54	+	-	+	-	+	+	+	+	+	III
30	56	++	-	++	-	++	+	++	+	++	III
31	46	++	-	++	-	++	+	++	+	++	III
Splenic Veins from Biopsy Specimens											
13	48	-	-	+	-	+	+	+	+	+	II
41	38	-	-	+	-	+	+	+	+	+	II
42	27	+	-	+	-	+	+	+	+	+	II
43	20	-	-	+	-	+	+	+	+	+	II
52	26	-	-	+	-	+	+	+	+	+	II
53	15	-	-	++	-	++	+	++	+	++	II
54	3	-	-	+	-	+	+	+	+	+	II
Angioma of Portal Vein											
55	19	-	+	-	+	+	+	+	+	+	I
Control Material											
49	38	-	-	-	-	-	-	-	-	-	I
50	20	-	-	-	-	-	-	-	-	-	I
S.V.		-	-	-	-	-	-	-	-	-	I
51 S.V.	44	+	-	+	-	+	+	+	+	-	II

P.V. Pressure
520 mm. water

KEY TO TABLE V.
Splenic and Portal Veins.

- = Normal

In columns 3 - 10:-

+ = Slight degree of hypertrophy

++ = Moderate hypertrophy

+++ = Marked hypertrophy (usually the most marked changes noted in the series)

NOTE

So far as possible these estimates were based on examination of portions of the veins where tangential cutting was not present. Changes visible on naked-eye examination were present only in the veins showing marked thrombosis (Nos. 1, 2 and 24), calcification (Nos. 1 and 55) and in two other cases (Nos. 21 and 41).

Cases Nos. 5 and 6

The portion of portal vein examined was attached to a piece of liver, a factor which introduces further variable factors in the changes produced in the vein.

It will be seen from study of the table that there is considerable variation in the picture found in each group so that a few further comments will be added to enlarge on the information contained in the table and the groups already described.

Case No. 1

In this case there was extensive eccentric intimal thickening with recent thrombosis. The adventitia was poorly defined and could scarcely be distinguished, while the most noteworthy feature of the section was the well-marked vascularity of the depths of the intima, which in one place contained a small arteriole (Fig. 14).

Case No. 3

There was thickening of all coats of the vein wall in one part of its circumference but little change in the vein wall in the other part. This was not due, so far as could be ascertained, to any folding of the vein wall or to the place of section.

Cases Nos. 5 and 6

The portion of portal vein examined was attached to a piece of liver, a factor which introduces further variable factors in the changes produced in the vein.

FIGURE 14.

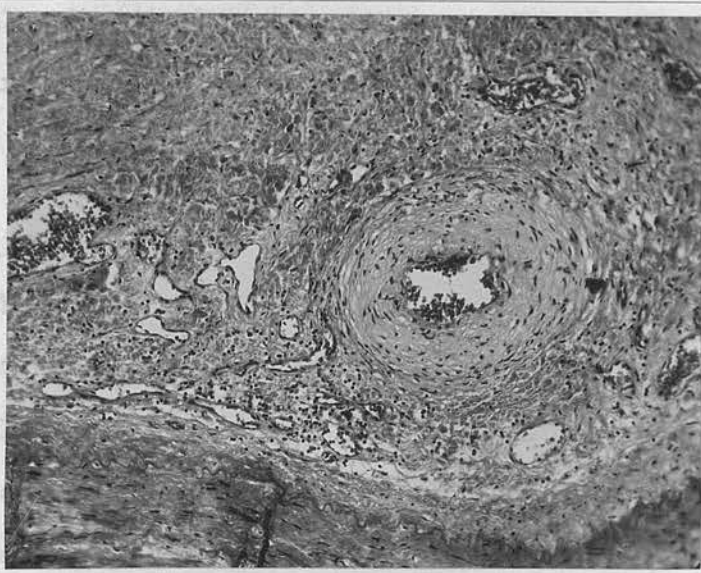


Figure 14 (X80) - Haematoxylin and Eosin: This shows well the vascularisation of the deepest part of the thrombus, a small arteriole being present in the section as well as numerous endothelial lined vascular spaces. The internal elastic lamina is seen running along the lower part of the photomicrograph.

These changes are similar to those noted and illustrated in this portion of the vein by MacMichael (1931). That the medial and internal changes are not a normal finding in this portion /

Case No. 24

This case belonged to Group 4. In it, the reduplication of the elastic tissue into the deepest portion of the intima was very marked though proliferation of elastic tissue in the media was not such a marked feature as in cases Nos. 1 and 2. In the intima there were one or two small areas of degeneration into which haemorrhage had occurred. Hypertrophy of the adventitial and medial muscles and the medial elastic tissue was present through the whole circumference of the vessel.

Splenic Veins from Biopsy Specimens

The changes in these veins showed certain characteristics. The adventitial muscle was usually very scanty in amount and adventitial hypertrophy of any marked degree was not seen. The changes in the medial muscle were more obvious but the slight hypertrophy noted in most cases was not considered marked enough to be of definite significance. Intimal changes were present in most cases and while they were composed of the same elements as the intimal changes noted in the portal and the more proximal portion of the splenic vein, they were localised very sharply in two cases (Nos. 42 and 43) to form raised plaques which jutted into the lumen of the vessel (Figs. 15 and 16).

These changes are similar to those noted and illustrated in this portion of the vein by McMichael (1931). That the medial and internal changes are not a normal finding in this portion /

FIGURE 15

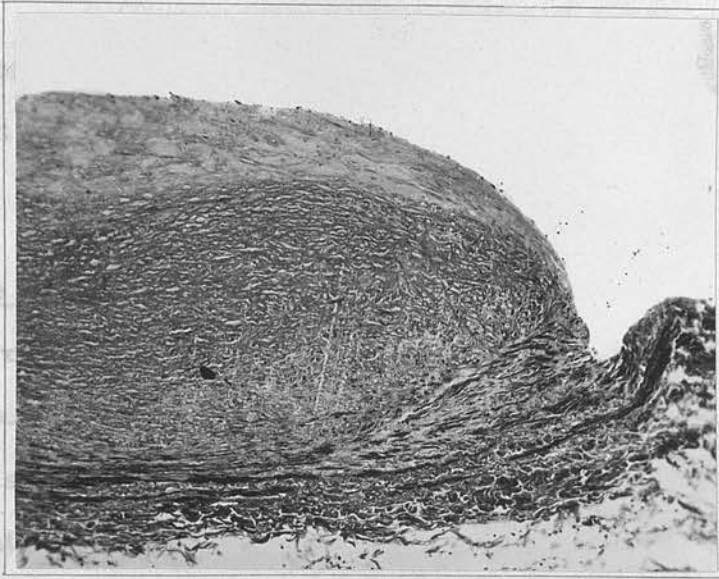


Figure 15 (X80) - Azan. (Case No. 43): The splenic vein to show the development of small muscle cells in the intima.

FIGURE 16

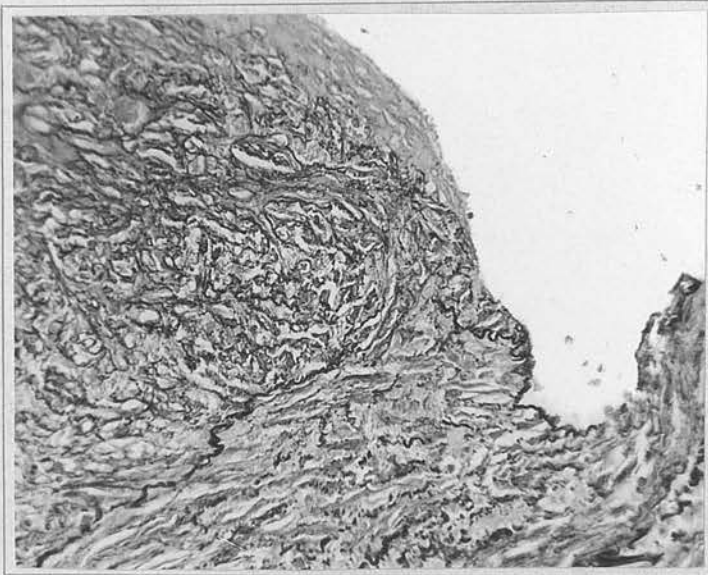


Figure 16 (X240) - Weigert and van Gieson (Case No. 43): A portion of the same field as illustrated in Figure 15 under higher magnification. It shows the development of numerous elastic tissue fibres in the intima.

These photomicrographs illustrate the well-localised nature of the intimal thickening beneath which is seen the slightly hypertrophied medial muscle and elastic tissue.

portion of the splenic vein was verified by the examination of a section from a control case.

Naked-Eye Appearances

Macroscopic abnormalities of the portal and splenic veins were noted as being present in all cases in which there was thrombosis or calcification. Tiny, raised flecks were noted in the intima of the portal and splenic veins in Cases No. 21 and 41.

Case No. 31

B.S. 6336. Male, age 17. Occupation, mechanic.

History:

Five years before operation the patient had an attack of infectious hepatitis. Five months and six months before operation he had two more attacks. At operation the spleen was removed, the pancreas in the splenic vein being reported as 120 cc. of water. The liver was thought to be normal. At the patient's return with 15 months after operation, it is possible that this is a case of splenic vein thrombosis though pathological changes were still present on x-ray examination two years after operation.

Case No. 34

B.S. 277. Female, age 39/12.

History:

The child was born fairly well and was six months old.

Four cases to which reference has not previously been made in this paper are included in Table V. A few details of these cases are given below:-

Case No. 52

L11.418. Male, aet. 26. Occupation: storeman.

History:

The patient had been increasingly dyspnoeic on exertion for three years and had had a dragging sensation in his left loin for three months. His spleen was palpable and was removed at operation when his liver was noted to be nodular. The patient has since remained well.

Case No. 53

D.B.6105. Male, aet. 17. Occupation: mechanic.

History:

Five years before operation the patient had an attack of infective hepatitis. Nine months and six months before operation he had haematemesis. At operation the spleen was removed, the pressure in the splenic vein being recorded as 320 mm. of water. The liver was thought to be normal. As the patient remains well 33 months after operation, it is possible that this is a case of splenic vein thrombosis though oesophageal varices were still present on X-ray examination two years after operation.

Case No. 54

L111.275. Female, aet. 3.9/12.

History:

The child had kept fairly well until she was nine months /

months old when it was noted that the abdomen appeared unduely prominent. She did not walk until she was a year old and when she developed whooping cough at the age of eighteen months her spleen was noted to be enlarged. Six weeks before operation she had a haematemesis and at operation the spleen was removed, the liver being so smooth and normal in appearance that no biopsy was taken and a diagnosis of splenic vein thrombosis made. Three months after operation the patient remains well.

Case No. 55

616/48. Female, aet. 19. Occupation: housework.

History:

Two years before death splenectomy was performed because of recurring haematemeses at the age of five, eight and thirteen years. At operation, the liver appeared normal and though X-ray a few months after operation demonstrated no oesophageal varices, two days before death, she had a final large haematemesis.

Liver (1600 g.):

Was pale but otherwise normal.

Microscopically: Apart from a slight "scattering" and shrinkage of the liver cells, possibly due to post-mortem autolysis, no abnormality was observed. In particular the lobular architecture was normal.

Splenic Vein: Contained several small raised, yellow flecks and patches of atheroma and also two small calcified plaques in its wall near its hepatic end.

Microscopically: A large, raised, calcified plaque occupied the superficial portion of a markedly thickened intima. Below this plaque and on either side of it, there was collagenous intimal thickening. This intimal thickening became less marked as the edges of the plaque were approached, where it was seen to contain a few small muscle cells. In its deepest portion there was considerable reduplication of elastic tissue but there was no definite internal elastic lamina nor was any trace seen of a medial or adventitial coat, the external layers of the vein consisting of loose collagenous, fibrous tissue and many small dilated vascular channels.

The hepatic end of the portal vein was replaced by a small mass of spongy-looking, red-brown material about 3 cm. in length. It emerged from this mass to break up into its normal branches.

Microscopically: /

Microscopically: Serial sections of this portion of the vein were cut in an endeavour to confirm the naked eye diagnosis of an angioma of the portal vein and to find out what happened to the portal vein in its course through the angioma.

The portal vein was followed into the mass where it was found to break up into two or three smaller branches. The portion of the portal vein entering the angioma did not possess a media, an adventitia or an internal elastic lamina and appeared to consist only of intima. The larger vessels in the mass presented a structure similar to this as did the numerous small blood channels of which the remainder of the mass was composed. The diagnosis of an angioma of the portal vein appeared to be substantiated by the presence of these spaces and by the absence of any trace of previous thrombosis of the portal vein and subsequent recanalisation.

The main branches of the portal vein in the angioma and the portal vein itself showed marked intimal changes. There was considerable intimal thickening throughout but more marked in some places than in others being especially well marked in the wall of the portal vein itself (Fig. 17). This thickening was caused by the presence in the subendothelial layer of small muscle cells (Fig. 18) running mainly in a longitudinal direction, surrounded by collagenous tissue and very numerous small elastic tissue fibres (Fig. 19). The latter two elements appeared to be present in inverse ratio to one another so that where the elastic tissue was most abundant, fibrosis was least marked, and vice versa.

Though these changes were most marked in the wall of the portal vein and to a slightly less extent, in its main branches, there was definite proliferation of elastic tissue and of muscles in the walls of the vascular spaces of the angioma, a finding which suggests that all these spaces communicated with one another or at least, were all subjected to the same increase in pressure.

These changes will be recognised as being the same changes which have already been noted as occurring in the intima of the portal veins and splenic veins examined. Some further comment on the significance of this finding will be made in the discussion.

FIGURE 17

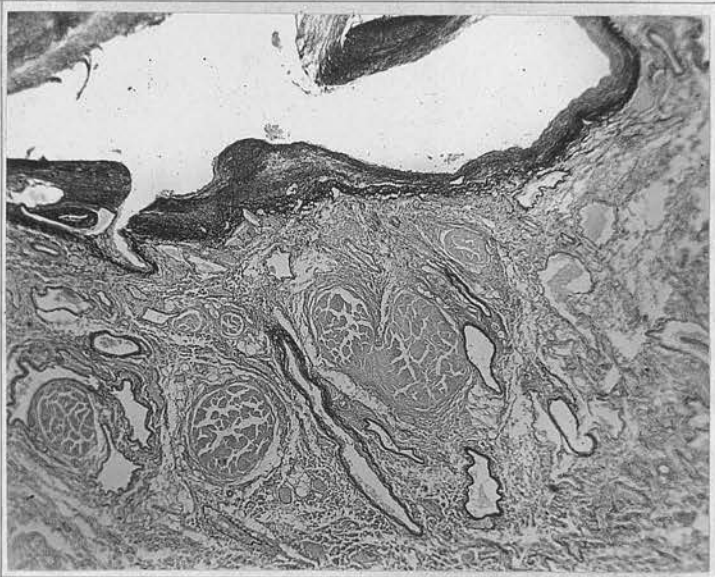


Figure 17 (X25) - Weigert and van Gieson (Case No. 55):
A low power view of the angioma showing a main branch of the
portal vein and several small vascular spaces in the walls of
which there is well-marked proliferation of elastic tissue.
The intimal thickening of the branch of the portal vein is also
seen to be rich in elastic tissue fibres (see Figure 19 for a
high power view of this).

Figure 19 (X125) - Weigert and van Gieson. The same view,
to show the proliferation of elastic tissue which has taken place
in the intima.

FIGURE 18

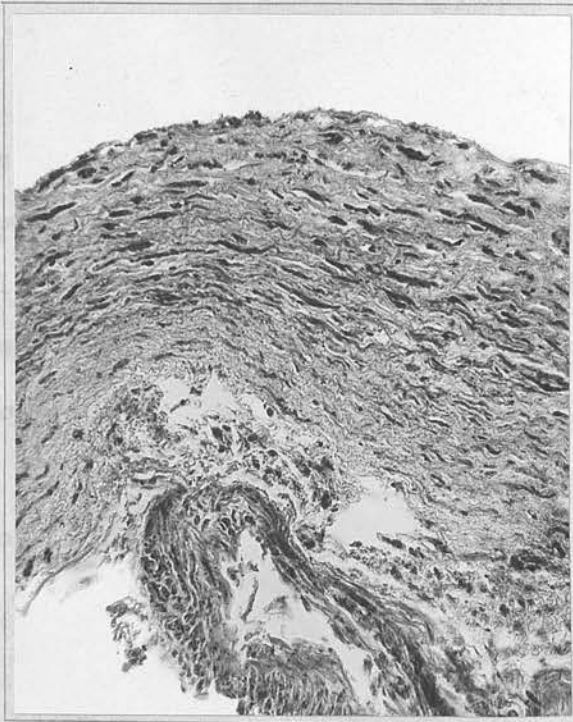


Figure 18 (X275) - Azan. (Case No. 55): A high power view of the wall of a branch of the portal vein in the angioma to show the proliferation of small muscle cells in the intima.

FIGURE 19

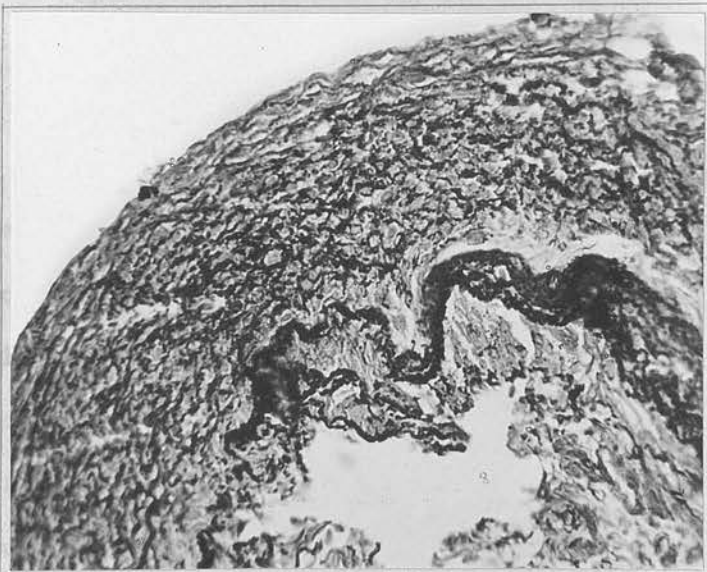


Figure 19 (X275) - Weigert and van Gieson: The same view, to show the proliferation of elastic tissue which has taken place in the intima.

DISCUSSION

Pei-Lin (1940) considered that, since he found veins with muscular hypertrophy and no intimal thickening but never veins with intimal thickening and no muscular hypertrophy, when there was an increase in pressure in the portal venous system, there was hypertrophy of the muscle layers followed by intimal thickening. This assumption derived additional support from comparison of the changes in the portal vein and in the tributaries which feed it, for in the latter, the changes are always less than in the portal vein and in them muscular hypertrophy only might be present while muscular hypertrophy and intimal thickening were present in the portal vein.

It will be seen from a study of Table V that these findings are borne out in the cases studied, Case No. 14 showing slight changes in the intima and muscular layers of the portal vein but none in the same layers in the splenic vein.

It is instructive to try to carry this scrutiny of the changes in the vein wall when the pressure in its lumen is increased a little further and to try to build up a picture of the successive changes which the vein wall undergoes.

Pei-Lin subjected the measurements he obtained of the degree of hypertrophy of the muscles in the vein wall to statistical analysis and found that in his 26 cases, the hypertrophy of the medial muscle could be regarded as statistically significant, while the hypertrophy of the adventitial muscle could not. The impression gained in this study has been that the increase in size and number of the adventitial muscles is /

is also significant in these cases.

The adventitia of veins is so loosely arranged that it is not easy to be sure that measurement of it is accurate for its boundaries are often difficult to define and hypertrophy of the muscle bundles appears to occur rather at the expense of the loose connective tissue between the muscle bundles than by any increase in width of the coat as a whole (Figs. 6, 8 and 10). The table shows too that in general, the hypertrophy of the muscle in the adventitia was of similar degree to that in the medial muscle. It is therefore suggested that in these veins definite hypertrophy of the adventitial muscles does occur.

Little mention is made by Pei-Lin of changes in the elastic tissue of the portal vessels but examination of the material indicates that changes in the elastic tissue of the media occur of the same degree as the accompanying hypertrophy of the medial muscles, in fact the increase in amount of elastic tissue present and an increasingly well-defined internal elastic lamina were often the first and most easily observed changes.

It is tempting to make a further point and suggest that those cases in which the elastic tissue changes in the media are most marked, amounting to an elastosis of the media, are those in which the increase in pressure has produced most change, the medial muscle being largely replaced by elastic tissue elements (Fig.13). That the medial elastic tissue changes were most marked in the cases showing extensive intimal thrombosis (Nos. 1, 2 and 24) would suggest further that the thrombosis was also a result of prolonged or excessive pressure in the portal vein. The very fact, however, that the maximum degree of /

of medial elastosis is associated with intimal thrombosis makes it difficult to decide what part in the pathological process these changes play, for the occurrence of thrombosis will, so obviously, depend on the interrelationship of many factors besides the presence of an increase in pressure in the vessel wall (Rosenthal, 1925; Evans, 1929; Simmonds, 1936 and Reich, 1942). It is not possible to say that the thickened thrombosed veins in Group IV are the end result of prolonged or high venous pressure though the fact that they show well-marked hypertrophy of their muscle coats and of their medial elastic tissue would seem to indicate that this might be the case.

Though Pei-Lin noted the frequent occurrence of small longitudinal muscle bundles in the intima in his series of pathological portal veins and suggested that these muscles might eventually become fibrosed and thus produce a thickened fibrous intima, he made little comment on any other intimal findings. McMichael (1934) had, however, described an increase in the amount of elastic and fibrous tissue in the intima of the portal vein in cases of hepatolienal fibrosis.

From examination of my own material it has been found that even where the intimal changes were minimal, as well as small muscle cells appearing in the subendothelial layer, thin strands of elastic tissue were present around these cells. In cases with more definite intimal thickening, small strands of collagen could also be seen, the intima being composed of these three tissues loosely arranged together.

As Weigert's elastic tissue stain is not entirely specific for elastic tissue it cannot be stated definitely that the tissue seen /

seen on examining these sections was elastic tissue, some of it might be thickened reticulum. However, the facts that the cases with most marked intimal thickening showed also the most definite new elastic tissue formation and that in arteries the intima, when subjected to stress, develops a musculo-elastic layer, suggest that the tissue which takes up the elastic tissue stain in these sections, is elastic tissue or its immediate precursor.

None of the sections examined was stained for fat but in none of them was there obvious atheroma with associated lipid changes present, a finding in keeping with Pei-Lin's observations. As, however, intimal thrombosis was such a marked feature in 3 cases (Nos. 1, 2 and 24), an attempt was made to determine what part the deposition of small thrombi on the vein wall played in the production of intimal thickening. Duguid (1946) has shown that intimal thrombosis and subsequent growth of endothelium over the clot, probably plays a part in the formation of atheromatous lesions in arteries and it does not appear unlikely that similar changes might occur in veins. In 10 cases (Nos. 3, 5, 6, 15, 16, 17, 19, 25, 41 and 52) red blood corpuscles were seen adhering firmly to the vein wall with, in one or two cases, apparent growth of endothelium over them. In the 3 cases showing gross thrombosis, the thrombosis appears to be superimposed on previous older thrombosis, for muscle walls and elastic tissue were not present in the eccentrically thickened portion of the vein which was composed of fibrous tissue with, in its depths, many small endothelial lined vascular spaces and in one case, a small well-formed blood vessel (Fig. 14). It is suggested /

suggested that this marked vascularity of the depths of the intima probably accounts for the infrequency with which degenerative intimal changes are noted, although the calcification present in Cases Nos. 1 and 55, is presumably the end result of some degenerative processes.

The appearance of well-localised plaques such as were seen to occur at the splenic end of the splenic vein might be due either to the presence of external anatomical factors or to thrombus formation. That changes occurring in the vein wall are largely influenced by mechanical factors either inside or outside the vein, is becoming increasingly widely recognised and the presence of some such factor, might be held responsible for the formation of the plaques. The presence of external supportive factors must be considered when an attempt is made to explain the eccentric thickening present in Case No. 3. The raised and well-defined nature of the plaques in the splenic vein suggest that thrombosis may have been a factor in their formation, though it is difficult to see how a previous thrombotic episode can explain the possession of muscle and elastic tissue in such a plaque. The presence of thrombosis only in the cases showing well-marked changes in the vessel walls would suggest that there is some relationship between the occurrence of thrombosis and intimal thickening.

The fact that the changes in the vein walls are influenced by factors other than merely an increase in venous pressure and that the lesions may be patchy in distribution, make it difficult to form any idea from histological study of the vessels how long the increase in pressure has been present, or how marked it has been. It should, however, be possible, by comparison of the changes /

changes in the portal and splenic veins in the same cases and by studying the apparent sequence in which changes occur, to identify the order in which they take place in these veins.

It has already been suggested that the first change is in the hypertrophy of the muscular coats of the media, the next stage being continuance of this hypertrophy along with an increase in depth of the subendothelial layer, patchy at first and then becoming more diffuse.

It has been suggested, though not substantiated, that thrombosis may, in some cases, be a terminal event in the chain of events brought about by an increase in pressure in the lumen of the vein. It would seem reasonable to suggest too, that where the hypertrophy of the medial and adventitial coats is more marked and the intimal thickening better defined, a further stage in the process has been reached than in those veins where the changes are not so marked. In this connection, Case No. 5 has been noted to show slight changes in the splenic vein and moderate changes in the portal vein.

It is therefore suggested that the groups into which these cases were divided for the purpose of description, do, in fact, represent successive stages in a process occurring in the wall of the portal vein in response to increased pressure in the vein. As far as possible, sections were taken from the same portion of the portal vein in all cases and, apart from Case No. 3, the changes in the vessel walls are fairly regular. Where several sections have been examined from different portions of the same vessel (e.g. No. 3), the changes have been found to be of roughly similar degree in all sections. The fact that changes in the splenic /

splenic vein were, on the whole, always slightly less marked than changes in the portal vein, also tends to indicate that the changes in any one section, especially when it is not taken from near any large branches, are probably a fairly good, though not completely sound, indication of the changes in the whole of that vessel. The groups, therefore, into which these cases are divided, as well as showing the sequence of events in these veins, may also give some indication as to the height or duration of the increase in pressure in them.

The question as to whether the changes that have been noted are in fact the result of an increase in pressure in the vein, was dealt with by Pei-Lin and McMichael (1934). They considered that this was so. It has, however, also been suggested that the changes are a result of a weakening of the vein wall by inflammatory processes (Fischer 1900, Warthin 1910 and Faber 1912) or nutritional disturbances. Simmonds (1912) distinguished a group in which the changes were due to syphilis. In none of the cases under consideration here is there evidence of an inflammatory process in the vein and since similar changes to those found to occur in this series are known to occur in veins where the pressure is definitely raised - as in an arteriovenous aneurysm (Hermannes 1923-1924) - it would seem that in these cases the changes are probably due to the increase in pressure.

The presence of nutritional factors leading to weakening of the vein wall and secondary changes in it are not so easy to rule out especially in association with a disease such as cirrhosis of the liver in which nutrition is now thought to play so large a part. In two of the cases (Nos. 54 and 55) examined, the liver was /

was normal but in neither of them does the section of portal vein show the picture of a hypertrophied vein such as has already been described. It may be, therefore, that nutritional factors do play some part but the similarity between the changes seen in the two cases examined and those in which the pressure is known to be increased is so striking that it is probable that the increase in venous pressure is the main factor. That there was an increase in pressure present would seem to be definite in the 17 cases in which there was evidence of the development of a collateral circulation in the shape of dilated oesophageal veins. Direct measurement at operation in Case No. 53 demonstrated the pressure in the splenic vein to be 320 mm. of water.

Study of Case No. 55 is of considerable interest for the vascular spaces of an angioma are lined by endothelium and a thin subendothelial layer, that is, have a structure similar to the intima of a vein. Apparently the similarity does not end there for the response of the vascular spaces to pressure is the same as that seen to occur in the portal vein, namely, development of small, longitudinally-arranged muscles with proliferation of elastic tissue and collagen in the subendothelial layer. Kaya (1907) suggested that the muscles which appear throughout the thickened intima of a hypertrophied vein, originate from the muscles of the media. Borst and Enderlen (1909) believed that they were derived from the cells of the intimal polster which is derived from the lining endothelial cells - a theory which has gained more general approval and which would appear to derive further support from the fact that the changes can occur in the absence of medial muscle.

CONCLUSIONS

It has been confirmed that cases of hepatolienal fibrosis show hypertrophy of the portal veins. The first change is slight hypertrophy of the medial and adventitial muscle coats and the medial elastic tissue. Next, there is further hypertrophy of these elements and some intimal thickening develops. This intimal thickening develops as a response to increased intravenous pressure and is equivalent to the development of the musculo-elastic layer found in arteries, being composed of longitudinal muscle cells, elastic tissue fibres and fibrous tissue. It is suggested that the changes in the vessel occur in the sequence suggested above, i.e., as described in Groups I - III. It is not so definite that the amount of change present in the vein wall is a reliable indication of the extent or duration of the increase in venous pressure though it is suggested this might be the case.

A fourth group of changes has been described in which thrombosis had occurred in veins already the seat of considerable hypertrophy of their walls. Little evidence of degeneration was present in the depths of the intima in this last group probably because of efficient vascularisation of the depths of the intima.

PART III

THE SPLEEN

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INTRODUCTION

It appears unlikely that advances in our knowledge of the significance of pathological changes in the spleen will be made until a better understanding of the function of that organ has been reached. At present little is known of the significance of the pathological changes which are met with in it but there are two main schools of thought in regard to the changes which occur in association with cirrhosis of the liver or obstruction in the portal or splenic veins.

One school, headed by McNee (1932), McMichael (1934 and 1935) and Menon (1938b), affirm that the splenomegaly often found associated with cirrhosis of the liver is due to the action of some toxin on the spleen producing hyperplasia of the splenic pulp. This toxin they suggest may be the same agent as was the cause of the liver damage or perhaps some toxin produced by the damaged liver. McMichael stresses the difficulty there is in producing splenomegaly in experimental animals by occlusion of the portal vein and points out that in man, cardiac disease of sufficient duration to cause changes in the spleen due to congestion, does not cause any marked degree of splenomegaly.

Menon (1938b) considered that the splenomegaly in these cases was produced by the same agent which, acting on the liver, produced cirrhosis and that the splenomegaly was in fact often precirrhotic.

The members of the staff of the Spleen Clinic at the Presbyterian Hospital in New York take the view that splenomegaly associated /

associated with cirrhosis of the liver is purely due to congestion (Larrabee, 1934; Whipple, 1945; Rousselot 1936; Rousselot and Thompson, 1939 and Rousselot, 1940) and quote in support of this view several cases of splenomegaly and typical Banti Syndromes caused by blockage of the portal or splenic veins and in the presence of a normal liver. McMichael (1934) had not been able to find any authenticated case of splenic anaemia or the Banti Syndrome in which there was no liver abnormality.

The splenomegaly may be due therefore either to an increase in portal pressure caused by cirrhosis of the liver or by blockage of the venous return of the spleen or it may be partly congestive and partly toxic.

Hueck (1928, 1929) quoted by Klemperer (1936) has suggested that whether or not splenomegaly develops as a response to congestion depends on the type of congestion present and states that congestion may be either active or passive. Passive congestion is caused by some central cause such as heart failure and in it, as McMichael observed, the spleen becomes acutely congested and there is venous stasis. Active congestion on the other hand is caused by blockage of the splenic or portal vein and here again there is acute congestion of the spleen, but as collateral channels develop which are not themselves congested, this congestion is not passive. The active hyperaemia present is said to be the cause of the hyperplasia of the pulp seen in these cases. This theory offers an explanation as to why chronic venous congestion does not cause marked splenic enlargement.

Both McNee (1929b) and McMichael (1931) consider that the periarterial haemorrhages, subsequent perivascular fibrosis and the /

the formation of siderotic nodules are the result of rupture of the splenic capillaries, probably where they join the small arterioles, the rupture being due to the increased venous pressure which is present in cases of cirrhosis of the liver or the Banti Syndrome. McMichael formed this opinion after examination by serial section of a spleen in which there were many siderotic nodules and from an examination of the correlation between the occurrence of haematemesis and siderotic nodules in the spleen.

In these cases the amount of splenic hyperplasia is said to depend to a large extent on the age of the patient, the ability of the splenic pulp to undergo hyperplasia being lost with increasing age (Kelsey et al., 1947). In addition to this factor the extent of the splenomegaly which occurs in cirrhosis of the liver and the Banti Syndrome depends, according to the same authors, on the duration and the extent of the increase in venous pressure and also on the presence of infarction, a spleen showing infarction being unable to increase in size to the same extent as one showing no infarction.

McMichael (1931) gives as the typical changes in the spleen in hepatolienal fibrosis

- (1) Distension of the sinuses.
- (2) Fibrosis of their walls.
- (3) Periarterial fibrosis.

He considers the changes in the Malpighian corpuscles to be mainly degenerative and of little significance depending again mainly on the age of the patient being more marked the older the patient. The occurrence of hyaline changes in the walls of the small /

small arteries of the spleen he found to be normal in adults.

The pathological changes which occur in the spleen in cirrhosis of the liver and the Banti Syndrome may therefore be entirely due to the presence of long-standing congestion and raised portal pressure, though in the opinion of some authors, the hyperplasia of the pulp may be due in part to the action on it of some toxin.

THE CASE MATERIAL

Spleens were examined from 45 cases of cirrhosis of the liver and three cases of blockage of the portal venous system. In two of the latter (Nos. 54 and 55) the clinical picture of a Banti Syndrome had been produced. In the examination of these cases particular attention was paid to the occurrence of hyperplasia of the pulp and the part it plays in the increase in the size of the organ and in the production of diffuse fibrosis, distension of the venous sinuses, the occurrence of periarterial lesions and their association with haematemesis and oesophageal varices. The results are given in table form and are thereafter discussed in more detail. One case of occlusion of the splenic vein (No. 56) has not been met with previously in this study and some details of this case are given.

TABLE VI - THE SPLEEN

Case No.	Sex	Age	Weight of Spleen in Grams					Pulp Hyperplasia	Sinus Hyperplasia	Diffuse Fibrosis	Fibrous Strands	Fibrosis around Sinuses	Distension of Sinuses	Peri-arterial Haemorrhage	Peri-arterial Fibrosis	Siderotic Nodules	Oesophageal Varices	Haematemesis	Liver	Portal Vein Changes
			0.200	2.400	4.600	6.800	800 →													
1	M	43						+	+	+	+	-	+	-	+	-	+	-	No fibrosis	IV
2	M	49						+	+	+	+	-	+	+	+	+	+	-	No fibrosis	IV
3	M	66						+	+	+	+	-	+	-	+	-	+	-	D.H.F.	III
4	F	34						+	+	+	+	-	+	+	+	+	+	-	Inf. Hepatitis	II
5	F	57			520			+	+	+	+	-	+	+	+	+	+	-	D.H.F.*	III
6	M	75			560			+	+	+	+	-	+	+	+	+	+	-	D.H.F.*	II
7	M	34	180		500			+	+	+	+	-	+	+	+	+	+	-	Cirrhosis	II
8	M	57						+	+	+	+	-	+	+	+	+	+	-	D.H.F.	III
9	F	72	140					+	+	+	+	-	+	+	+	+	+	-	Cirrhosis	I
10	F	75						+	+	+	+	-	+	+	+	+	+	-	Cardiac Cirrhosis	I
11	M	47	80					+	+	+	+	-	+	+	+	+	+	-	Cardiac Cirrhosis	II
12	M	77	180					+	+	+	+	-	+	+	+	+	+	-	Cirrhosis	II
13*	M	48						+	+	+	+	-	+	+	+	+	+	-	Cirrhosis	III
14	F	72						+	+	+	+	-	+	+	+	+	+	-	No fibrosis	III
15	M	29						+	+	+	+	-	+	+	+	+	+	-	Cardiac Cirrhosis	II
16*	M	29						+	+	+	+	-	+	+	+	+	+	-	P.N.S.	III
17	M	19						+	+	+	+	-	+	+	+	+	+	-	D.H.F.*	III
18	M	53						+	+	+	+	-	+	+	+	+	+	-	D.H.F.*	III
19*	F	62						+	+	+	+	-	+	+	+	+	+	-	D.H.F.*	III
20	F	24						+	+	+	+	-	+	+	+	+	+	-	P.N.S.	III
21	F	37						+	+	+	+	-	+	+	+	+	+	-	D.H.F.*	III
22	F	51						+	+	+	+	-	+	+	+	+	+	-	Cardiac Cirrhosis	II
23	M	63	120					+	+	+	+	-	+	+	+	+	+	-	P.N.S.	III
24*	M	60						+	+	+	+	-	+	+	+	+	+	-	D.H.F.*	IV
25	M	44						+	+	+	+	-	+	+	+	+	+	-	P.N.S.	III
26	F	64						+	+	+	+	-	+	+	+	+	+	-	D.H.F.*	III

TABLE VI - THE SPLEEN
(continued).

Case No.	Sex	Age	Weight of Spleen in Grams					Pulp Hyperplasia	Sinus Hyperplasia	Diffuse Fibrosis	Fibrous Strands	Fibrosis around Sinuses	Distension of Sinuses	Peri-arterial Haemorrhage	Peri-arterial Fibrosis	Siderotic Nodules	Oesophageal Varices	Haematemesis	Liver	
			0.200	2.400	4.600	6.800	800→													
27	F	54		230				+	+	+	-	-	+	-	-	-	-	-	Cardiac Cirrhosis	II
28	F	39		380				+	+	+	-	-	-	-	-	-	-	-	P.N.S. or C.C.	II
29	F	54		220				+	+	+	-	-	-	-	-	-	-	-	Inf. Hepatitis	II
30	M	56		250				+	+	+	-	-	+	-	-	-	-	-	P.N.S.	III
31	M	46		220				+	+	+	-	-	+	-	-	-	-	-	Cirrhosis	II
32	M	46		380				+	+	+	-	-	+	-	-	-	-	-	D.H.F.*	
33	F	74	120					+	+	+	-	-	+	-	-	-	-	-	D.H.F.	
34	M	62	160					+	+	+	-	-	+	-	-	-	-	-	Cardiac Cirrhosis	
35	F	46		350				+	+	+	-	-	+	-	-	-	-	-	Cardiac Cirrhosis	
36	M	58		200				+	+	+	-	-	+	-	-	-	-	-	D.H.F.*	
37	F	79						+	+	+	-	-	+	-	-	-	-	-	Cirrhosis	
38*	M	27						+	+	+	-	-	+	-	-	-	-	-	P.V. Pressure 250 mm. of water	
39*	M	29						+	+	+	-	-	+	-	-	-	-	-	Cirrhosis	
41*	M	38						+	+	+	-	-	+	-	-	-	-	-	P.N.S.	
42*	M	27						+	+	+	-	-	+	-	-	-	-	-	P.N.S.	
43*	M	20						+	+	+	-	-	+	-	-	-	-	-	P.N.S.	
45*	F	60						+	+	+	-	-	+	-	-	-	-	-	Cirrhosis	
49	M	38						+	+	+	-	-	+	-	-	-	-	-	Cirrhosis	
50	F	20	120					+	+	+	-	-	+	-	-	-	-	-	Cirrhosis	
51	F	44	100					+	+	+	-	-	+	-	-	-	-	-	Normal	I
52*	M	26						+	+	+	-	-	+	-	-	-	-	-	Normal	I
53*	M	15						+	+	+	-	-	+	-	-	-	-	-	Fatty	II
54*	F	3	150					+	+	+	-	-	+	-	-	-	-	-	Cirrhosis	
55*	F	17						+	+	+	-	-	+	-	-	-	-	-	? Normal	
56	M	43						+	+	+	-	-	+	-	-	-	-	-	Normal	

Column 1. * Professor Sir James Learmouth's cases.
+ See next page.

KEY TO TABLE VI
The Spleen.

D.H.F. = Diffuse hepatic fibrosis - diagnosed
microscopically.

D.H.F.* = Diffuse hepatic fibrosis - diagnosed
naked-eye.

P.N.S. = Post-necrotic scarring.

Cirrhosis = Type of cirrhosis not determined.

Cases in column 1 = marked with an asterisk, represent a
selected series of cases sent to
Professor Sir James Learmonth for
operative treatment.

NOTE

So far as possible an attempt was made to decide
definitely whether certain changes were or were not present
and this is indicated by + or - . Where the changes
were present but slight in amount this is indicated by $\frac{+}{-}$.
Where the sinuses were distended to 2-3 times their normal
size this is indicated thus ++.

Case No. 56

M.H.A.2734. Male, aet. 43. Occupation: not given.

History:

The patient had been ill with progressive abdominal distension and oedema for about two months before admission. He finally became comatose and died of acute pyelonephritis and bronchopneumonia. There was a carcinoma of the pancreas which had spread to involve both the splenic artery and vein markedly narrowing the lumen of the vein which was practically completely occluded.

Liver

Was of normal size and shape but contained a few scattered tumour nodules 1 cm. in diameter.

Distension of the sinuses

Examination of the 5 cases showing an atrophic liver changes reveals that distension of the venous sinuses of the pulp is a prominent feature in them all and in Case No. 56, where the spleen is not markedly enlarged and the blockage of the splenic vein probably of fairly recent origin, it is the only notable pathological change present. It was found difficult to decide in many cases whether the venous sinuses were distended or, when sinus hyperplasia (Laver, 1924; Kasperer, 1928; and Jasper, 1931) was present, the sinuses were all round an oval in shape. The presence of definite distension of the sinuses was accepted when they were dilated to 2-3 times their normal size (shown in the /

DISCUSSION

It will be noted that the presence of 3 cases in this series (Nos. 54, 55 and 56) in which the liver showed no cirrhosis, gives an opportunity to compare and contrast the changes seen in the spleen in obstruction of the portal or splenic vein with those seen in cases showing cirrhosis of the liver. If any notable difference emerges from study of the findings in these two sets of cases, it would be reasonable to suggest that this might be due to the action of a toxin acting on the spleen in the cases of cirrhosis of the liver, while, if no marked difference emerges, this would suggest that the changes which occur in the spleen in association with cirrhosis of the liver are entirely due to obstruction to the venous return of the spleen by the presence of cirrhosis of the liver.

Distension of the Sinuses

Examination of the 3 cases showing no cirrhotic liver changes reveals that distension of the venous sinuses of the pulp is a prominent feature in them all and in Case No. 56, where the spleen is not markedly enlarged and the blockage of the splenic vein probably of fairly recent origin, it is the only notable pathological change present. It was found difficult to decide in many cases whether the venous sinuses were distended as, when sinus hyperplasia (Duerr, 1924; Klemperer, 1928; and Jaeger, 1931) was present, the sinuses were all round or oval in shape. The presence of definite distension of the sinuses was accepted when they were dilated to 2-3 times their normal size (shown in the /

the table as '++'). Sinuses, too, which were definitely dilated often had around them a slight but definite fibrosis and the presence of this, added confirmatory evidence that there was distension of the venous sinuses, presumably of some standing.

As will be seen from Table VI, this definite distension of the sinuses is not always associated with an enlarged spleen for in 5 cases in which there was definite distension of the sinuses, the spleen weighed less than 400 g. while in 7 cases it weighed more than 400 g.. It also does not appear to be associated with the age of the patient for 4 cases with definite distension of the sinuses were over 40 and 8 were under 40 years of age. The relatively large number of cases under the age of 40 is largely due to the presence in the series of 14 cases (marked '*' in the table) which had been sent to Professor Sir James Learmonth because of splenomegaly or haematemesis for operative treatment. These cases introduce, whenever they occur in this study, a possible source of error in any statistical analysis, for they represent a highly selected group of cases, usually in young people in whom clinical evidence, often in the shape of haematemesis, of a damaged liver or a Banti Syndrome was given some time before the onset of liver failure which in the older patient was often the first indication that liver disease was present.

In 4 cases there was distension of the sinuses in the absence of oesophageal varices, though in 8 cases this additional evidence of increased portal pressure was also present.

Hyperplasia of the Pulp

The fact that in most of the cases studied there is hyperplasia of the splenic pulp with the development of many new sinuses in it (sinus hyperplasia) and a diffuse fibrosis suggests that these three processes take place at roughly the same time. Case No. 6, however, shows very well-marked hyperplasia but no diffuse fibrosis, while Case No. 13 shows a diffuse fibrosis with little hyperplasia of the pulp. It is difficult to know what significance to attach to these findings but they would suggest that the sinus hyperplasia accompanies and is an immediate result of hyperplasia of the pulp for the two always occur together, while the diffuse fibrosis may be the result of some other factor, such as increased venous pressure acting on the sinuses - whether they are newly formed or not.

During examination of the sections some difficulty was experienced in defining diffuse fibrosis, for the formation of definite fibrous tissue is often not very marked in these cases. It was found that in the cases which showed a diffuse fibrosis there was replacement of the normal splenic pulp by venous sinuses between which ran narrow bands of collagenous tissue in which were found scattered fibroblasts. In the most marked cases small strands of fibrous tissue were found between the sinuses and this accentuation of the diffuse fibrosis has been noted in the table.

Periarterial Lesions /

Periarterial Lesions

It has already been noted that McMichael (1931) found a direct relationship between the occurrence of haematemesis and siderotic nodules (in 8 out of 16 cases of hepatolienal fibrosis). This relationship holds good in 3 of the 5 cases in this series in which siderotic nodules were present in the spleen. In one case, though haematemesis had not occurred, oesophageal varices were noted to be present. In only one case (No. 52) was the relationship not noted and in this case information was not complete. In 5 cases periarterial haemorrhage was present without siderotic nodules but as only one section was examined in most of these cases, these findings are probably of little significance and the results in this series confirm McMichael's and McNee's views as to the mode of origin of these nodules.

It is not easy to exclude the action of some toxic substance as the cause of the weakening of vessel walls giving rise to periarterial haemorrhage and to haematemesis, in fact Menon (1938b) considered the periarterial fibrosis to be mainly toxic in origin. However, the two cases of the Banti Syndrome (nos. 54 and 55) in which there is no reason to believe a toxic factor to be present, both showed haematemesis as one of their first symptoms and in one (No. 54) well-marked siderotic nodules were seen in the spleen. These findings add further support to McMichael's and McNee's view that these haemorrhages are due to an increase in venous pressure.

On examination of these cases an impression was gained that not all perivascular fibrosis was due to antecedent perivascular fibrosis, /

fibrosis, for the fibrosis around the vessels was often slight and loose in formation occurring in 16 out of 26 cases without any concurrent periarterial haemorrhage. It would appear probable, therefore, that in some of these cases at least, the periarterial fibrosis occurs unconnected with organised periarterial haemorrhage.

Peri-Malpighian fibrosis was noted to be present in 4 cases (Nos. 24, 35, 52 and 55) and is probably due to ischaemia of the peri-Malpighian area from interference with the blood supply to the Malpighian corpuscles, an area supplied by the penicillar arteries running from the Malpighian corpuscles. Support is given to this hypothesis by its occurrence in association with definite small infarcts (No. 35).

Age

In order to find out if there was a definite relationship between the age of the patient and the degree of splenomegaly present, a graph was constructed in which the weight of the spleen was plotted against the age of the patient. It will be seen from this graph (Fig. 20) that there is a definite tendency for the spleen to be smaller in the older cases even though in many of them, as death was due to liver failure, the same maximum degree of liver change was presumably present. This tendency for the weight of the spleen to be related to the age of the patient also held good in the cases of infective hepatitis (indicated in the graph by black dots) and in the cases designated as cardiac cirrhosis (shown as a cross and circle in the table). Age, would, therefore, appear to be a very /

FIGURE 20

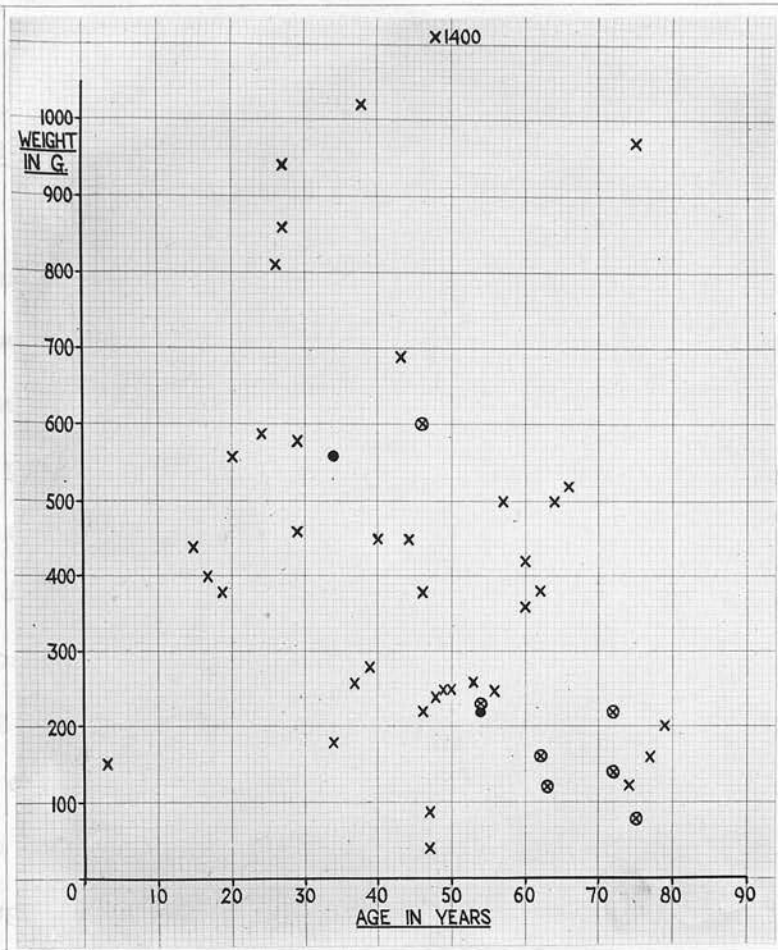


Figure 20: Relationship between weight of spleen and the age of the patient in cases of cirrhosis of the liver. Note the tendency for the size of the spleen, no matter what the cause of the cirrhosis, to be smaller in the older patients.

- ⊗ Cases of cardiac cirrhosis.
- Cases of acute cirrhosis following infective hepatitis.
- x Cases of cirrhosis.

very important factor in deciding the extent to which a spleen can enlarge, though, as will be discussed later, many other factors are also concerned.

Congestion - active and passive.

It is not easy to see how the results obtained in this study can be used to verify Hueck's (1928-29) views on the pathogenesis of splenic changes due to congestion, for all the cases studied were selected because of the derangement of the lobular pattern of their liver and therefore contain no cases of pure, passive congestion. The cases of cardiac cirrhosis showing distortion of the lobular architecture will produce conditions leading to the addition of an active element to the existing passive congestion and thus the possibility of further splenic enlargement.

The only way in which it appears possible to explain the splenomegaly in Case No. 35 is on the basis of Hueck's views and that in it there was active congestion caused by the distortion of the liver architecture due to the presence of a so-called cardiac cirrhosis. A part of added interest and one which will be returned to again later is that this patient was definitely hypertensive. If this explanation is correct it adds further support to the hypothesis that the appearance of the liver in this case, does represent an abnormality of liver structure.

Correlation of the Findings in the Liver, Portal Vein and Spleen.

1. The Liver and Portal Vein

Cases of definite cirrhosis classified as old-standing diffuse hepatic fibrosis with coarsely nodular livers and cases placed in the category of post-necrotic scarring and cirrhosis without fibrosis, all show well-marked changes in the walls of the portal veins. It would appear to be established, therefore, that definite cirrhosis of the liver, whether or not fibrosis is present, produces changes in the portal vessels and an increase in pressure in them.

Study of the remainder of the material from the liver and portal vein does not afford much further information of value. In both cases of infective hepatitis the changes in the portal vein were noted as belonging to Group II, while in the 5 cases of cardiac cirrhosis in which the portal veins were studied, 3 were classified as showing Group II changes and 2, Group I changes in the portal veins. Five of these cases, therefore, show the presence of pathological changes in the portal veins, changes which, whether due to disruption of the lobular architecture or cardiac failure, are due to congestion. Of the cases labelled as cirrhosis of unknown type, 2 showed Group III changes in the portal vein and 3, Group II changes - that is, they all showed evidence of slight or definite changes in the portal vein.

2. Portal Hypertension and the Changes in the Veins

It is not easy to decide what finding can be taken as definite /

definite evidence of the presence of an increase in pressure in the portal vein (portal hypertension). The production of ascites depends on many variable factors and it is proposed to accept McMichael's (1934) criterion of evidence of the establishment of a collateral circulation, as a definite indication that portal hypertension was present in a particular case.

Early evidence of its presence will be given by the presence of dilated oesophageal veins. It is of some interest to note, at this point, that in my own personal experience, evidence of the establishment of a collateral circulation in the shape of dilated haemorrhoidal veins (McIndoe, 1928) has not been found.

Study of the 31 cases in which liver, portal vein and spleen were all available for examination shows that in all the cases where oesophageal varices were present, whether or not there was haematemesis, marked changes (Group III or Group IV) were noted to be present in the portal vein. This finding adds further proof to the assumption made previously in Part II that these changes in the vein were in fact due to an increase in pressure in their lumen.

The fact that all 3 cases showing Group IV changes in the portal vein, i.e., with portal vein thrombosis, showed well-marked oesophageal varices, while many veins showing Group III changes had no varicosities, would tend to bear out the suggestion already made in Part II that the changes noted in the portal vein as Group IV changes are, in fact, a further stage of the changes noted in Group III.

3. Portal Hypertension and the Changes in the Spleen

If the cases in this series which show dilated oesophageal veins and well-marked pressure changes are plotted on a graph (Fig. 21) the weight of spleen against age of patient, there is such a wide scatter that it is difficult to imagine that the splenomegaly in these cases is a purely congestive process. From this it could be inferred that the splenomegaly in these cases is not entirely due to the presence of congestion though a much larger series of cases would need to be examined before a definite pronouncement could be made on this relationship. The fact that spleens weighing more than 600 g. were present without the occurrence of either haematemesis or oesophageal varices (Nos. 6, 35 and ? 52) would also serve to indicate that the relationship between the occurrence of congestion and splenomegaly is not a direct one.

Haematemesis occurred in no patient in this series who was over 50 years of age, though oesophageal varices were present in 5 patients, and in only one case (No. 6) over 50 years of age, was the spleen larger than 600 g.. It is, therefore, apparent that neither marked splenic enlargement nor haematemesis was common in patients over this age perhaps because, though there is an increase in portal vein pressure, reflected in the occurrence of Group III changes in the portal vein in 9 cases over 50 years of age, these patients have lost the ability to adapt themselves to this increase in pressure by the development of an efficient collateral circulation.

FIGURE 21

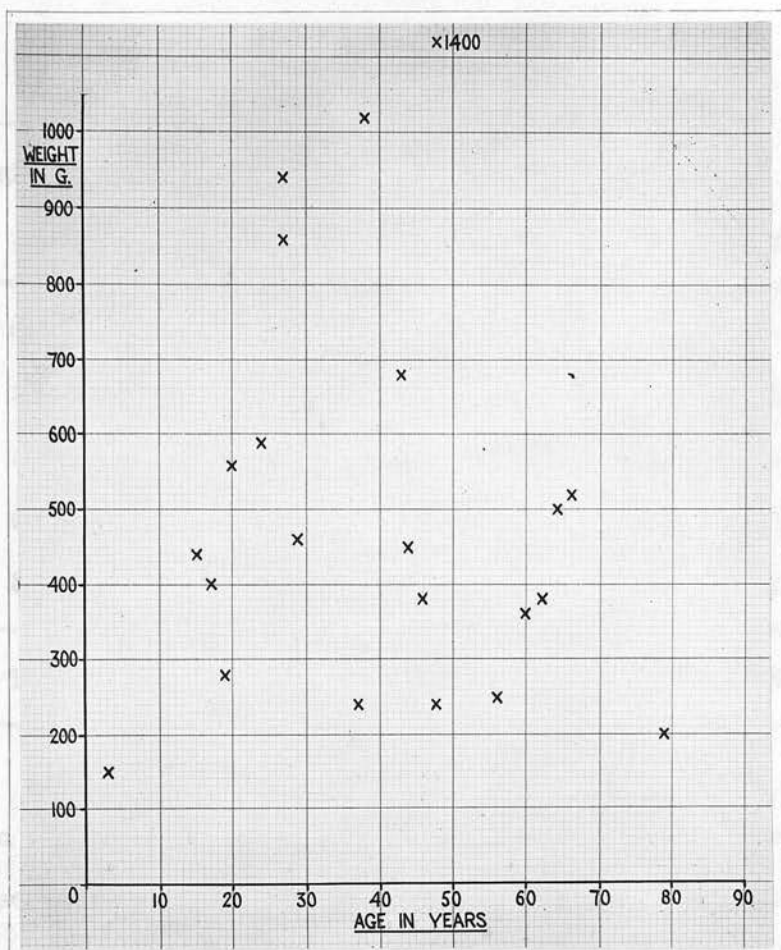


Figure 21: Relationship of weight of the spleen to the age of the patient in those cases where there were either varicose oesophageal veins or in which there had been a haematemesis. The marked scatter in those cases suggests that the splenomegaly is not purely a congestive process but depends in addition on other factors.

TABLE VII

Relation of Changes in the Portal Vein
to the Size of Spleen

Weight of Spleen in grams	Changes in the Portal Vein			
	Group I	Group II	Group III	Group IV
0 - 199	4	3	1 (No.11)	-
2 - 399	-	6*	7	1
4 - 599	-	1*	7 ^x	-
6 - 799	-	-	-	1
800 —	-	1 (No.6)	-	1
Totals	4	11	15	3

In Part II, when the changes in the portal vein were discussed, it was suggested that though it was established that the appearance of definite changes in the portal vein indicated the presence of an increased pressure in their lumen, it was more doubtful whether the groups into which the material was divided were an indication of the amount or duration of that increase in pressure. However, for various reasons, which have received some corroborative evidence in this chapter, it was considered that /

* Includes one case of Infective Hepatitis.

^x Case No. 8, complicated by the presence of Hodgkin's Disease, is omitted.

that these groups might indicate such variations.

With these facts in mind, the changes in the portal vein were examined and related to the weight of the spleen, the results shown in Table VII being obtained. As we have seen, Group III and Group IV changes can both be assumed to be due to markedly raised portal pressure, both because of their microscopic features and since in these cases which show them, other evidence of portal hypertension are often present. Also, since the complete significance of Group IV cases is not very clear, the occurrence of thrombosis depending on so many different factors, a more accurate picture of the relationship between the changes in the portal vein and the increase in the size of the spleen would probably be obtained if Groups III and IV were run together.

When this is done, it can be seen that there appears to be a direct relationship between the amount of change in the portal vein and the weight of the spleen and this relationship becomes accentuated if Cases Nos. 6 and 11 are disregarded, for in them the changes present are so different from those seen in the rest of the cases examined that they may be considered separately.

Case No. 11 (Male, aet. 47) showed no hyperplasia of the pulp of the spleen nor any of the changes seen in the other cases with congestion, the spleen being completely atrophic and yet Group III changes are present in the portal vein. Case No. 6 (Male, aet. 75) is the converse of this in that there were only slight changes present in the portal vein (Group II), but marked hyperplasia of the splenic pulp without fibrosis or any other evidence of congestion. It is probable that in the latter /

latter case the factor which caused the liver damage, perhaps fairly soon before death, also affected the spleen in this marked fashion (cf. Menon, 1938b).

TABLE VIII

Relation of Changes in the Portal Vein
to the Size of Spleen
(amended version of Table VII).

Weight of Spleen in grams	Changes in the Portal Vein		
	Group I	Group II	Groups III and IV
0 - 199	4	3	-
2 - 399	-	6	8
4 - 599	-	1	7
6 - 799	-	-	1
800 →	-	-	1
Totals	4	10	17

Though with these two cases removed, there is a definite relationship between the changes present in the portal vein and the weight of the spleen, their occurrence, especially the marked hyperplasia present in Case No. 6, demonstrates that in some cases at least, other factors besides congestion determine the extent of the splenomegaly. Since the factors operating in these two cases may be present in minor degrees affecting the extent /

extent of the splenomegaly in all the cases it was not considered that connecting the weight of the spleen to the different body weights would add any further useful information.

Study of Table VII has shown that the degree of splenomegaly is usually related to the extent of the changes in the portal vein and though other factors which influence the splenomegaly causing atrophy (No. 11) or hyperplasia (No. 6) also play an unknown and presumably variable part in the production of this splenomegaly. The same factor that causes the changes in the vein appears to be responsible for a large part of the splenomegaly. What exactly this factor is, is not so easy to determine for it may be either the degree or the duration of the congestion and portal hypertension. Unfortunately, in the cases which have been studied there is no way in which the relative effect of these two factors can be distinguished.

4. The Type of Cirrhosis and the Changes in the Portal Vein and in the Spleen

(a) The Portal Vein

	<u>Changes in the Portal Vein</u>			
	<u>Group II</u>	<u>Group III</u>	<u>Group IV</u>	<u>Total</u>
Post Necrotic Scarring:	1	6	2	9
Diffuse Hepatic Fibrosis:	1	8	1	10

The type of cirrhosis present, whether it be post-necrotic scarring or diffuse hepatic fibrosis, does not, in this small series, appear to affect to any extent, the changes noted in the vein /

vein and the degree of portal hypertension. This conclusion derives additional support from the frequency with which haematemesis occurs in both types - in 7 cases of each type.

(b) The Spleen

	<u>Weight of Spleen in Grams</u>		
	<u>Under 400</u>	<u>Over 400</u>	<u>Total</u>
Post Necrotic Scarring:	3	8	11
Diffuse Hepatic Fibrosis:	9	4	13

There would, however, appear to be a significant difference in the degree of splenomegaly which results from the two types of cirrhosis of the liver, post-necrotic scarring being more liable to produce marked splenomegaly. This finding, taken in conjunction with the fact suggested above, that the changes in the portal vein do not appear to be determined by the type of cirrhosis, would indicate that the factor which caused the post-necrotic scarring probably also affected the spleen directly.

5. The Role of Congestion in the Production of Splenomegaly

It has been shown that the extent of the splenomegaly which occurs in association with cirrhosis of the liver is closely related to the degree or duration of the congestion in that particular case, but that it also depends on the type of cirrhosis present and on the age of the patient. The degree of splenomegaly in cases of the Banti Syndrome will depend only on the congestion and on the age of the patient but as this syndrome occurs almost entirely in young people and by its very nature is usually /

usually fatal before middle age is reached, age is not such an important factor in these cases and will not limit the extent of the splenomegaly.

There are 3, possibly 4 (No. 53), cases of splenic congestion with a non-cirrhotic liver in this series and examination of them shows that the main features of established portal hypertension and congestion are, distension of the sinuses, some hyperplasia of the pulp, a diffuse fibrosis and periarterial lesions, all of these changes being found also in cases of cirrhosis with splenomegaly. It is not easy to be sure when there is definite hyperplasia of the splenic pulp for in these cases no normal pulp tissue is present and it is mainly on account of the marked increase in the size and the weight of the organ, that hyperplasia is known to be present. In none of the cases with a "normal" liver was the splenomegaly marked so that it would appear that congestion due to blockage of the splenic vein flow can only produce a moderate degree of splenomegaly - a finding which adds support to McMichael's (1934) conclusions that when the spleen is enlarged to more than 450 g. some other factor beside congestion must be present.

The ultimate weight of the spleen will therefore, in all cases, depend on the ability of the spleen to undergo hyperplasia - this decreasing with age - and also the amount of hyperplasia present initially. Whether hyperplasia has been present or not, there is distension of the sinuses with the ultimate production of a fine diffuse fibrosis of the splenic pulp.

These conclusions support those drawn by Menon (1938b) who considered /

considered that the splenomegaly which accompanied damage to the liver produced by various chemicals was caused mainly by the toxic action on the spleen of the same factor and those of Cameron and de Saren (1939) who marsupialised the spleen in a rat thus dissociating it from the portal circulation and any effects of increased pressure in the portal vein, administered carbon tetrachloride, producing cirrhosis of the liver and splenomegaly.

These experiments were performed using chemical poisons. What effect a pure dietetic deficiency will produce on the spleen after producing cirrhosis of the liver will have to be worked out in experimental animals and until more is known about the factors causing human cirrhosis, it will be difficult to evaluate correctly the relative importance of congestive and toxic factors in the production of splenomegaly.

The weight of the spleen in these patients, as well as depending on the age, the degree of congestion and probably its duration, appears to be determined by the type of cirrhosis of the liver with which it is associated, the spleen in 8 out of 11 cases of post-hepatic cirrhosis being only 4 out of 13 cases of diffuse hepatic cirrhosis weighing more than 100 g. Though in a small series of cases this may be a chance finding it is nevertheless an interesting observation. The high incidence of splenomegaly in cases of post-hepatic cirrhosis may be due to the action of the spleen on the factor causing the liver damage.

The definite relationship between the progression of

CONCLUSIONS

Although the results obtained in this study have provided the basis for a great many comments they do not, mainly on account of the relatively small number of cases on which they are based, enable many definite conclusions to be drawn.

It has been confirmed that the extent of the splenic enlargement in cases of cirrhosis of the liver and the Banti Syndrome depends on the age of the patient and that in cases of cirrhosis of the liver the splenomegaly is largely due to the increase in portal pressure, i.e., it is congestive in nature. It has been pointed out too, that this latter relationship is not an entirely direct one and is influenced by the pressure of other factors, principally hyperplasia of the splenic pulp.

The weight of the spleen in these patients, as well as depending on the age, the degree of congestion and probably its duration, appears to be determined by the type of cirrhosis of the liver with which it is associated, the spleen in 8 out of 11 cases of post-necrotic scarring (but only 4 out of 13 cases of diffuse hepatic fibrosis) weighing more than 400 g.. Though in a small series of cases this may be a chance finding, it is nevertheless one of considerable interest. This high incidence of splenomegaly in cases of post-necrotic scarring may be due to the action on the spleen of the factor causing the liver damage.

The definite relationship between the occurrence of haematemesis /

haematemesis and the presence of oesophageal varices and well-marked changes in the portal vein, is a factor of some value in establishing the significance of the changes in the portal vein already noted in Part II.

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INTRODUCTION

Several cases of acute PART IV obstruction of the portal vein

ACUTE VASCULAR LESIONS IN THE PORTAL VEIN AND HEPATIC ARTERY

Department. These cases form an interesting little group and afford an opportunity to discuss the effects of acute vascular

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lesions both on the spleen and the liver for an understanding of the effects caused by acute and chronic obstruction of the portal vein. Splanic vein and hepatic artery is an essential

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preliminary to the study of the normal physiology and pathology of the changes which occur in cirrhosis of the liver and the

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Banti Syndrome.

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splenic veins were discussed and this chapter serves to complete

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spleen and the vessels connecting them. It also links up the previous chapter with the following chapter where the mechanisms by which the raised venous pressures are produced will be discussed.

INTRODUCTION

Several cases of acute obstruction of the portal vein and hepatic artery have been seen recently in the Pathology Department. These cases form an interesting little group and afford an opportunity to discuss the effects of acute vascular lesions both on the spleen and the liver for an understanding of the effects caused by acute and chronic obstruction of the portal vein, splenic vein and hepatic artery is an essential preliminary to the study of the normal physiology and pathology of the changes which occur in cirrhosis of the liver and the Banti Syndrome.

In the previous chapter the changes which occur in the spleen as a result of chronic obstruction in the portal or splenic veins were discussed and this chapter serves to complete the study of the changes which take place in the liver, in the spleen and the vessels connecting them. It also links up the previous chapter with the following chapter where the mechanisms by which the raised venous pressures are produced will be discussed.

Obstruction of these vessels produces the well known Banti's Syndrome originally described by Banti (1893) and discussed in subsequent reports by Ross (1909), Armstrong and Garms (1914) and Kelley and Comfort (1945). In it the main findings are congestion of the liver lobules with collagenous changes around the central veins and slight fibrosis around the portal tracts. Though no cases of this syndrome are available for study it will be recognised that a similar effect can be produced /

produced by the increased A. Liver to the outflow of blood from the liver found in cardiac failure and produced

Owing to its double blood supply occlusion of one afferent vessel does not, provided an efficient collateral circulation is available and the other vessel is unaffected, cause true infarction (Haberer, 1906; Zimmerman, 1930; Pass, 1935) and true healed infarcts of the liver are exceedingly rare (Lund, Stewart and Liever, 1935). So-called 'pseudo-infarcts' (Winternitz, 1911) are much more common and occur when one vessel is inefficient and the collateral circulation is inadequate. In them there is no necrosis and they take the form of small, pale, usually wedge-shaped areas of liver tissue - often just below the surface of the organ - composed of atrophic cells, the cells often showing marked fatty changes.

The results of occlusion of the main hepatic vessels have been noted in various experimental animals and verified in human pathological material (Winternitz, 1911; Cameron and Mayes, 1930).

if the portal vein is also occluded, of a coagulative necrosis (Lund, Stewart and Lieber, 1935)

(1) Hepatic Veins

Occlusion of these vessels produces the well known Chiari's Syndrome originally described by Budd (1846) and discussed in subsequent reports by Hess (1905), Armstrong and Carnes (1944) and Kelsey and Comfort (1945). In it the main findings are congestion of the liver lobules with collagenous changes around the central veins and slight fibrosis around the portal tracts. Though no cases of this syndrome are available for study it will be recognised that a similar effect can be produced /

produced by the increased resistance to the outflow of blood from the liver found in cardiac failure and produced experimentally in animals by Bolton (1914), Zimmerman and Hillsman (1930), Bolton and Barnard (1931) and Day and Armstrong (1940).

(2) Portal Vein

When a main branch is occluded there is some atrophy of the centrilobular cells in the area supplied, with eventual slight atrophy of the lobules concerned. There may be necrosis of centrilobular cells but unless there is blockage of the intralobular veins, a true infarct does not occur.

(3) Hepatic Artery

Here, when the collateral circulation is adequate (and the area affected is small), there is some death of centrilobular liver cells, but when larger areas are affected, a true infarct is produced with whole lobules affected and the production, if the portal vein is also occluded, of a coagulative necrosis (Lund, Stewart and Lieber, 1935).

B. Spleen /

B. Spleen

When the portal vein is occluded there is obstruction to the blood flow from the spleen and from the intestines. Although many experiments have been performed to ascertain the result of occluding the blood flow from the spleen and to determine the role of congestion and increased pressure in the splenomegaly of the Banti Syndrome acute obstruction of the portal vein in man is usually superimposed on an older lesion so that, the obstruction being at first gradual, a collateral circulation has time to develop.

Both Menon (1938a) and McMichael (1934) attempted to produce gradual obstruction of the portal vein in animals but succeeded only in producing either acute venous infarction or slight splenomegaly with subsequent atrophy of the pulp.

In thrombosis of the main trunk of the portal vein, the principal and most urgent effect is on the return of blood from the intestines, congestion and infarction of the bowel being the principal cause of death in these cases. If this effect is to be avoided an Eck fistula must be established before obstruction of the portal vein. When the splenic vein is occluded the effect of the congestion is only on the spleen and if the obstruction is affected slowly enough, a collateral circulation can open up and, as has already been noted, a congestive splenomegaly (Rousselot, 1936) is produced because of the active congestion present (Hueck, 1928-29). If the obstruction to the splenic vein is rapid there will be acute congestion and venous infarction.

THE CASE MATERIAL

Nine cases which came to post-mortem in the latter half of 1948 will be described. They consist of:-

5 cases of portal vein thrombosis

2 cases of hepatic artery thrombosis

1 case with ischaemic lesions in the liver

1 case of angioma of the portal vein already

described in Part II (Case No. 55)

Two of the cases also show the presence of older infarcts in the spleen. They are studied mainly to demonstrate the pathological changes which occur in the liver and the spleen when these vessels are occluded. Following their description points of interest arising from them will be discussed in detail.

History:

The patient had complained of epigastric pain and vomiting for two months before death. Jaundice developed and the liver enlarged. Case No. 57

390/48. Female, aet. 29. Occupation: housewife.

History:

Two weeks before death the patient was delivered of a full time child. The delivery was normal. Four days before death she developed acute epigastric pain and at post-mortem there was gangrene of the small bowel due to thrombosis of the superior mesenteric vein.

Liver (1400 g.):

Was pale and soft showing no obvious intrahepatic thrombosis. The portal vein at the point where the superior mesenteric vein joined it and the superior mesenteric vein itself, contained ante mortem thrombus as did the left branch of the portal vein. The superior mesenteric artery was normal.

Microscopically: /

Microscopically: There was a slight diffuse pallor of the parenchymal cells, most marked around the central veins. The lobular architecture was normal though it was difficult to make out because of pallor and a slight scattering of the cells, the cells being all separated from one another and at no place appearing in cords. Many of the liver cells contained two nuclei. Early thrombosis was present in one portal vein but the other portal veins were normal and none showed any abnormality of their walls.

Spleen (100 g.):

The cut surface was light in colour.

Microscopically: Apart from some patchy congestion there was remarkably little abnormality. In particular there was little post mortem change, a fact which suggests that the changes in the liver may not be entirely due to autolysis. There was no increased fibrosis.

Case No. 58

397/48. Male, aet. 78. Occupation: retired engine-driver.

History:

The patient had complained of epigastric pain and vomiting for two months before death. Jaundice developed and the liver enlarged, the cause of death being an intra-hepatic bile duct carcinoma.

Liver (2780 g.):

Was considerably enlarged and finely nodular. It was deeply bile-stained. Both branches of the portal vein and its main trunk were distended with tumour tissue, tails of this tissue extending into the splenic and superior mesenteric veins. The bowel was normal.

Microscopically: Scattered throughout there were very many small tumour nodules usually situated in portal tracts. These nodules had produced compression and slight distortion of the lobular architecture. The liver cells contained considerable quantities of bile pigment but were otherwise normal. The portal veins were also normal.

Spleen (220 g.):

Section revealed a probable slight increase in the amount of fibrous tissue present.

Microscopically: /

Microscopically: There was slight prominence of Billroth's cords with, under the capsule, distension of the sinuses and a slight early diffuse fibrosis.

History:

Case No. 59

409/48. Male, aet. 59. Occupation: department manager.

History:

For about 20 years the patient had been known to have a duodenal ulcer and pyloric stenosis. The day before death a partial gastrectomy was performed and after operation his general condition appeared to be good. Next evening he had a slight haematemesis, collapsed and died in about 10 minutes. The patient was a known diabetic and received insulin daily.

Liver (1500 g.):

Showed no abnormality apart from the presence of a small hemispherical red infarct, 2 cm. across the base, situated below the capsule in the left lobe.

The portal vein and its main branches were completely thrombosed though the splenic and superior mesenteric veins contained no clot and there was no evidence of infarction of the bowel or melaena.

Microscopically: The hepatic parenchyma distant from the infarct showed only pallor of the centrilobular cells. The infarct was situated immediately below the capsule of the liver and consisted of a mass of red blood corpuscles around which the liver lobules showed centrilobular necrosis with hyaline changes in the liver cells and a marked polymorphic reaction. The portal veins were markedly congested but contained no definite ante mortem thrombus.

Spleen (120 g.)

Appeared normal.

Microscopically: The only abnormality noted was the presence of a slight patchy congestion with an opening out of the sinuses. There was no increased fibrosis.

Case No. 60 /

Case No. 60

463/48. Female, aet. 65. Occupation: housewife.

History:

The patient was admitted with severe biliary colic 2 weeks before her death. As she was too ill for any major surgical procedures to be performed on her, cholecystostomy was performed, but she died of obstruction and inflammation of her common bile duct and a hepatorenal syndrome.

Liver (not weighed):

Was soft and flabby. There was some accentuation of the normal lobular architecture but there was no definite necrosis or cholangitis. The major bile ducts were slightly dilated. The portal vein in the edge of the lesser omentum was completely occluded by a large moderately adherent, ante mortem thrombus. This thrombus extended a little way into the liver but not into the splenic or mesenteric veins which appeared normal. The bowel was normal.

Microscopically: There was considerable postmortem change with extracellular oedema, degeneration and "scattering" of the cells into small clumps so that the lobular architecture was not easily seen. This scatter was most marked in the centrilobular areas where there was some congestion, and the cells contained a few small round cells, polymorphs and usually 2-3 small bile ducts.

Spleen (90 g.):

Was noted as being slightly soft.

Microscopically: There was no abnormality apart from the presence of a few scattered fibroblasts through the pulp.

Case No. 61

490/48. Female, aet. 58. Occupation: housewife.

History:

The patient was admitted for investigation of pain in the abdomen and back. She had marked oedema of the legs and signs of renal infection. Death was due to peritonitis, probably originating from an acute pyelonephritis.

Liver (1400 g.) /

Liver (1400 g.):

There was a large purple area (10 x 5 x 3 cm.) involving the anterior and inferior surfaces of the left lobe. In this area were several smaller yellow areas 2 - 3 cm. in diameter. There was no evidence of the presence of chronic venous congestion or abnormality elsewhere in the liver. The coeliac axis and all its main branches were extensively thrombosed. This thrombosis did not extend into the intra-hepatic branches of the hepatic artery. The small bowel was congested and infarcts were present in stomach and spleen. The portal vein was normal.

Microscopically: An irregular area of liver tissue showed necrosis of its cells which had a deeply staining hyaline appearance with nuclear loss but little polymorphic infiltration or blood in this area. This area was surrounded by a zone of polymorphonuclear cells and adjacent to it, there was an area which showed slightly less marked cellular changes, the changes being most marked in the centrilobular areas and accompanied by a marked polymorph response. Section from the left lobe showed no abnormality apart from some centrilobular congestion. The branches of the hepatic artery were markedly congested.

Spleen (140 g.):

Contained several small yellow wedge-shaped infarcts.

Microscopically: Two sections were examined. In one there was an area of well marked disruption and congestion of the pulp due to recent infarction, while in the other the congestion was much less marked and the pulp contained many polymorphonuclear cells, but was otherwise normal.

Case No. 62

498/48. Male, aet. 42.

History:

This patient had complained of indigestion for many years before admission to hospital. Medical treatment for four weeks did not alleviate his symptoms and he began to vomit so a partial gastrectomy was performed. The patient died five days later from broncho-pneumonia and centrilobular necrosis. Before operation he was markedly hypertensive (blood pressure 230/128) but after operation his systolic blood pressure was 70 mm. Hg.

Liver (1900 g.) /

Liver (1900 g.):

Was soft and the right lobe showed more pallor than the left. The portal vein was normal.

Microscopically: The changes in the left lobe were much more marked than those in the right. In both there was centrilobular necrosis with no cellular reaction around but with slight small round cell reaction in the portal tracts. In the left lobe only small islands of normal liver cells remained around the portal tracts and the cellular reaction in these portal tracts was more marked than in the right lobe. The remaining liver cells showed slight fatty change. The vessels were normal.

Spleen (180 g.):

Contained several small firm dark areas about 0.6 cm. in diameter suggestive of the presence of infarction.

Microscopically: Several small areas of splenic pulp were packed with red blood corpuscles with no normal splenic tissue visible, while the remainder of the organ showed acute congestion and a slight cellular reaction, mainly composed of plasma cells.

Case No. 63

586/48. Female, aet. 51. Occupation: housewife.

History:

Two years before death the patient had a bout of severe epigastric pain and jaundice three days before death. She had a similar attack with a terminal haematemesis. Death was due to thrombosis of the superior mesenteric artery and infarction of the small bowel.

Liver (1900 g.):

Was soft and flabby with a small triangular infarct 2 cm. across the base, composed of white cartilaginous looking tissue on the surface of the right lobe. Apart from slight congestion no further abnormalities were noted. The main trunk of the coeliac axis was partially occluded by well organised thrombus but the hepatic and left gastric arteries appeared normal: the splenic artery contained an old thrombus: the superior mesenteric artery showed patchy atheroma and the ilæocolic artery contained some partially organised thrombus.

Microscopically: The 'infarct' was seen as a homogeneous deeply/

deeply eosinophilic plaque situated apparently outside the capsule of the liver. The liver tissue below the plaque showed slightly more marked centrilobular degeneration with loss of nuclear staining than in the other section examined from a point distant from this area. In the second section there was moderately well marked centrilobular congestion and fatty changes in the centrilobular areas. The liver architecture was normal. Below the plaque there was a slight excess of fibrous tissue with a well formed capsule running below the plaque and splitting on either side as if to enclose it completely though the superficial covering was not present in the section. The portal tracts showed a slight excess of fibrous tissue and a marked small round cell infiltration by lymphocytes and plasma cells. The hepatic arteries showed hyperplastic sclerosis. The portal veins were normal.

Spleen (90 g.):

Was shrunken and distorted because of the presence of numerous small fibrous scars probably representing old infarcts.

Microscopically: There was acute congestion with occasional small areas in which the pulp showed a diffuse fibrosis - presumably ischaemic in origin.

Comment:

The presence in this case of old infarcts in the bowel and spleen and the presence of a large loosely attached thrombus in the proximal portion of the aorta make it appear probable that the area noted in the liver was, in fact, a "healed" infarct.

Case No. 64

MHA.2770. Female, aet. 47. Occupation: housewife.

History:

About 45 hours before death the patient had severe abdominal pain followed by melaena and haematemesis. At operation 24 hours after the onset of the pain 5 ft. of gangrenous bowel was removed. Venous thrombosis of the superior mesenteric vein, extending into the portal vein, was found at postmortem.

Liver:

Was slightly diminished in size with the lobular pattern not /

not easily seen. It was very soft and the intrahepatic radicles of the portal vein were all extensively thrombosed. The portal vein, superior mesenteric, ilioocolic, inferior mesenteric and midcolic veins were all filled with blood clot.

Microscopically: There was marked autolytic change present throughout the section. The centrilobular cells contained many small brown granules and a few scattered cells showed fatty changes. There was no abnormality of the lobular architecture. The portal veins were distended and contained small portions of recent ante-mortem thrombus. In view of the presence of autolytic changes, it was not easy to distinguish whether there was centrilobular necrosis, but the impression was gained that centrilobular necrosis was present. The liver lobules appeared to be slightly smaller than usual.

Spleen:

Was enlarged to twice its normal size and was noted to contain two small firm pale infarcts.

Microscopically: There was a rather patchy diffuse fibrosis of the pulp, most marked in the subcapsular regions where many of the sinuses were distended. Two large pale areas were seen in which there was loss of splenic structure and around which there was a zone of active fibrosis and cellular reaction. A few small areas of normal splenic tissue were also seen and many of the veins contained recent thrombus while one vein contained an old, completely organised thrombus.

DISCUSSION

(1) Acute Portal Vein Thrombosis.

In 3 (Nos. 57, 59 and 64) of the 5 cases of portal vein thrombosis the duration of the thrombosis can be fairly accurately deduced from the case history. Case No. 59, where the thrombus probably originated at operation 24 hours before death, showed what are presumably the earliest changes with a small area of haemorrhage and centrilobular necrosis in the surrounding lobules, while elsewhere in the liver, there was only slight centrilobular degeneration. The bowel and the spleen both appeared normal.

In Case No. 64, thrombosis had occurred about two days before death. Marked post mortem autolysis was present with scattering of the liver cells, the impression being gained however that the changes were most marked in the centrilobular areas. The bowel was infarcted and there was evidence of older thrombosis in intrasplenic branches of the splenic vein.

In Case No. 60, the lesions in the liver were roughly similar to those seen in No. 64, but here the bowel was normal while a few fibroblasts were present in the splenic pulp. This latter finding was probably associated with the jaundice, circulatory disturbance in the liver and the obstruction of the common bile duct.

Case No. 57, where the symptoms from the portal vein thrombosis had been present for four days showed no definite centrilobular necrosis, only a scattering of liver cells similar to that seen in Case No. 60. The bowel was infarcted but the spleen /

spleen showed only a patchy congestion.

No significant changes were noted in the liver cells in Case No. 58, where partial portal vein thrombosis must have been present for some time. That the obstruction was not complete was indicated by the fact that there was no infarction of the bowel. In this case there was an early diffuse fibrosis of the spleen probably again associated with intrahepatic obstruction of vascular channels, this time of about two months' duration.

Study of these 5 cases does not reveal any definite, easily recognisable pattern of liver changes in acute thrombosis of the portal vein. At first it was considered that this might be due to the thrombus not completely occluding the vein in some cases. However, even in the two cases in which there was infarction of the bowel and where the obstruction in the portal vein was presumably nearly complete, the changes in the liver were not the same in both cases.

It is interesting to note that in 2 cases (Nos. 55 and 57) there was a slight scatter of the liver cells, while a similar appearance coupled with more definite post-mortem changes was present in Case No. 60. Although it is difficult to determine how much of the scatter was due to the presence of post mortem autolysis, it is worthy of note that it did occur in these 3 cases of portal vein thrombosis.

Case No. 62 is instructive in that the changes noted to be diffusely present - more marked in the left lobe of the liver than the right - were similar to the centrilobular necrosis seen in 2 cases (Nos. 59 and 61) of portal vein thrombosis. The drop in blood pressure from a systolic pressure of 230 mm. of mercury to /

to a systolic pressure of only 70 mm. of mercury with subsequent diminution in blood flow, would appear to be sufficient explanation for the occurrence of the centrilobular necrosis. That the changes were more marked in the left lobe would suggest that either the left lobe had anyway a less efficient blood supply than the right or that the changes were due, in part at least, to a deficiency of cystine, which is known to be present in smaller amount in the blood draining from the large intestine to the left lobe of the liver (Copher and Dick, 1928). It will be remembered that this patient had been troubled by a peptic ulcer for some time before death so that it is probable that his diet had been deficient in many respects.

(2) Thrombosis of the Hepatic Artery

The 2 cases in which thrombosis of the hepatic artery occurred show an early infarct in one (No. 61) and a healed infarct of the liver in the other (No. 63). There was death of a considerable area of liver tissue in the patient with the early infarct who died mainly from thrombosis of the mesenteric artery and gangrene of the bowel. In Case No. 63 there were numerous old infarcts present in other organs and though it is difficult, from microscopic examination, to be quite sure that the small pale area noted on the surface of the liver was a healed infarct, its appearance along with the presence of old healed infarcts in other organs would suggest that this is so. Healed infarcts of the liver were noted by Lund, Stewart and Lieber (1935) to be extremely rare and at the time of their report they could only find one case recorded in the literature, to which they added a case /

case of their own.

(3) Effect of Portal Vein Thrombosis on the Spleen

The effect of portal or splenic vein thrombosis on the spleen when the thrombosis was of long standing, has been discussed in the previous chapter. Study of the 5 cases of portal vein thrombosis described here demonstrates the effect of more acute thrombosis on the spleen. When secondary effects due to obstruction of intrahepatic vessels by the primary disease process, which in two cases lead to the portal vein thrombosis, are disregarded, the main effect is to cause acute congestion of the whole organ (Nos. 57 and 59). Later (No. 64) this may proceed to necrosis of small areas of splenic tissue and the formation of small venous infarcts,

The eventual result of portal vein thrombosis, if immediate death from mesenteric thrombosis does not occur, has been shown (Winternitz, 1911) to be atrophy of the liver lobules with diminution in the size of the organ. This can be seen either when an Eck fistula has been established first of all or when only one branch of the portal vein is occluded. Despite the long standing portal obstruction present in Case No. 55, sufficient to give rise to very marked portal hypertension, the liver weighed 1600 g. and these changes were not seen so that in this case, sufficient blood must have passed the obstruction to avoid the occurrence of hepatic damage. In Case No. 64 however, the liver was noted to be diminished in size and microscopically the lobules were considered to be smaller than normal.

CONCLUSIONS

Acute obstruction of the portal vein causes death from infarction of the bowel, produces acute congestion of the spleen and in some cases, centrilobular necrosis of liver cells. In other cases a "scattering" of liver cells was noted, but owing to the similarity between this appearance and the changes produced by post-mortem autolysis, the significance of this finding is doubtful.

Thrombosis of the hepatic artery causes death of an area of liver tissue and the production of a true infarct. A case with a healed infarct of the liver has been described.

In the spleen, thrombosis of the portal vein or splenic vein, causes acute congestion and may, if death does not occur at once, produce small venous infarcts.

Portal vein occlusion of long standing, if marked enough, will produce atrophy of the liver and a decrease in size of the liver lobules.

INTRODUCTION

In the first three chapters **PART V.** pathological changes

which **EXPERIMENTAL AND THEORIES OF PORTAL HYPERTENSION.** of

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INTRODUCTION

In the first three chapters the pathological changes which occur in the liver, portal vein and spleen in cases of cirrhosis of the liver and the Banti Syndrome have been discussed. The changes which have been seen to occur in these organs are very largely a result of an increase in pressure in the portal vein, this increase in pressure being due either to intrahepatic or extrahepatic blockage of that vessel. In this chapter it is proposed to discuss mainly the changes in the liver and how they lead to portal congestion and hypertension.

An essential preliminary to this study is a knowledge of the normal anatomy of the liver and in particular, its vascular supply. The cases presented in Part IV act therefore as an introduction to this chapter, the first part of which will deal with the normal blood supply and anatomy of the liver; the changes in the vascular supply which occur in cirrhosis, will then be discussed.

In order to verify previous work on this subject and to enable a few personal opinions to be developed on these subjects, several normal and cirrhotic livers obtained at postmortem were injected with Neoprime Latex and the casts thus obtained studied.

Why the changes in the vascular pattern in cirrhosis of the liver should give rise to portal hypertension has produced considerable controversy in the past without any very definite reason for its occurrence being put forward. The aim of the chapter will be to discuss, in the light of the findings in the injection /

injection specimens and the cases already studied, the various theories which have been advanced.

The Normal Anatomy of the Liver

The liver develops around the two vitelline veins and the vitelline sinusoids between the two umbilical veins. It is formed originally from a diverticulum which is budded off from the floor of the future duodenum (Arey, 1940). In the adult, the liver parenchyma is in the form of a delicate mantle which is draped over the hepatic veins with portal tracts grouped around the periphery (Opie, 1904) so that liver lobules are formed. From the portal tracts sinusoids run out to the hepatic veins, each sinusoid being lined by a single layer of liver cells, on the other side of which is a small bile channel. A regular and delicate structure is thus formed, each bile channel and sinusoid being separated by a liver cell.

The liver has a double blood supply, oxygen being brought to it by the hepatic artery and nutriment from the intestine for metabolism by the portal vein. Burton-Opitz (1911c) described the hepatic artery as supplying the fibrous framework of the organ, i.e., mainly the portal tracts and their vessels. It carries about 30 per cent of the blood which is supplied to the liver (Macleod and Pearce, 1914) and also some pre-urea bodies for detoxication (Herrick, 1905).

Olds and Stafford (1930) showed that as well as supplying blood to the portal tracts and the vessels running in them, the hepatic artery supplied blood to the peripheral end of a few sinusoids. They affirmed that the peripheral end of each sinusoid /

sinusoid is supplied by a branch of the portal vein or hepatic artery but never by both and that the emptying of the narrow branch of the hepatic artery into the relatively large sinusoid is the factor which finally reduced the hepatic arterial flow to the same pressure as that of the portal vein. The two different blood streams do not mix till the sinusoids anastomose nearer the centre of the lobule.

The pressure of the blood in the hepatic artery is presumably that of the systemic circulation, i.e., about 120 mm. of mercury, while the pressure in the portal vein is usually taken to be 10 - 20 mm. of mercury (McIndoe, 1928) so obviously the high pressure in the hepatic artery will be at least partially reduced before it mingles with the blood from the portal vein. By the time the blood from the hepatic artery reaches the terminal capillaries and escapes into the peripheral ends of the sinusoids, considerable reduction in pressure will have been effected, but considerable interest has been taken in this question of how the pressure in the two capillary circulations are equalised for, as will be discussed later, the amount of blood flowing through one or other of these vessels is said to affect the amount of blood flowing through the other (Burton-Opitz, 1911a). As we have seen already, Olds and Stafford (1930) considered that the emptying of the narrow capillary of the hepatic artery into the relatively wide sinusoid was one of the main factors in reducing the pressure.

The Blood Supply of the Cirrhotic Liver

Various authors have postulated some anastomosis in the portal tracts between the hepatic artery and portal vein (Sabourin, 1885; McMichael, 1932; Moschcowitz, 1948) and the theory has been advanced that it is an upset in this anastomosis so that the blood from the portal vein meets the blood from the hepatic artery before the pressure has been reduced which causes the portal hypertension present in all well-established cases of cirrhosis of the liver.

Herrick (1907) in perfusion experiments, showed that the amount of fluid returned through the portal vein was more readily varied by variations in the amount of fluid perfusing through the hepatic artery in the cirrhotic than in the normal liver. Burton-Opitz (1911a) and Pearce and Macleod (1914) considered that the amounts of blood flowing through the portal vein and the hepatic artery were closely related and that the flow through one was regulated to a slight but definite extent by the flow through the other.

In cirrhosis of the liver the upset of this relationship may play a part in the production of portal hypertension and as Christian (1942) pointed out, if this relationship is important, the relative pressures should be still more distorted in cases with hypertension in their systemic circulation. The association of cirrhosis of the liver and systemic hypertension is, however, so rare, that this has never been verified.

McIndoe (1928) demonstrated by means of further perfusion experiments that blood flowing through the portal veins in a cirrhotic liver did not reach the liver cells for collateral channels /

channels developed proximal to the terminal branches to the sinusoids. At a pressure of 10 - 20 mm. of mercury only 13 per cent of the portal vein flow could be collected from the hepatic vein, the remainder flowing out through collateral channels. In the nodules of regenerated liver tissue present in cirrhotic livers the central veins have been pushed aside till they are incorporated in the portal tracts and using gelatine as an injection mass, he found that when the injection penetrated the nodule at all it was through the hepatic artery and not through the portal vein. He suggested, therefore, that in the cirrhotic liver there was no deficiency of blood but that the blood did not reach the liver cells which, though not deficient in number, were deficient in blood supply. In these cases an artificial Eck fistula was present, death being due to liver failure usually precipitated by failure of the systemic circulation. In support of this conception it has been noted that the total blood supply to the cirrhotic liver is not markedly diminished (Kretz, 1905). McNee (1932) claimed to have noted hypertrophy of the hepatic artery in cases of cirrhosis of the liver though McIndoe (1928) did not observe this.

In the normal liver injection of the portal vein and the hepatic artery demonstrates a regularly branching portal vein along with which, often spiralling slightly round it, runs the much smaller hepatic artery. As McIndoe showed in his macerated injection specimens of the vascular tree this regular arrangement is upset in cases of cirrhosis of the liver with dissociation of the portal vein and hepatic artery trees so that they lose their normal close relationship to each other.

It was recognised by Kretz (1905) that it was upset of the regular arrangement of the liver cells which was the primary change in cases of cirrhosis of the liver, nodules of regenerated liver cells being formed which, in the process of development, pushed the central vein to one side of the lobule.

The part played by the development of fibrous tissue in the cirrhotic process has been debated by various authors. Kretz (1905) suggested that in cases of cirrhosis of the liver, there was hypertrophy of the hepatic artery to supply the newly formed fibrous tissue, while McIndoe (1928) considered that it was the sclerosing effect of this fibrous tissue on the portal veins which caused diminution in their vascular bed.

Though Burton-Opitz (1910, 1911b, c; 1912a, b, c, d, e, f; 1914) and McMichael (1932) showed that the blood flow to the liver was under vasomotor control it is difficult to assess how important a factor this control is in producing variations in the blood flow to the liver. In recent years attention has been drawn to the part played by veins in various circulatory disorders, (McMichael (1948) considering that the primary disorder responsible for the production of congestive cardiac failure is in the veins. It may be, therefore, that the vasomotor control of the portal vein plays a more vital part in the production of the vascular disorders which accompany cirrhosis of the liver, than has been realised.

Though, as has been noted already, the flow of blood through the portal vein is thought to depend to some extent on the flow through the hepatic artery, probably the main factor which regulates the amount of blood flowing through the portal vein /

vein is the flow through the splenic and mesenteric arteries.

An increase in the flow to the mesenteric artery occurs after food and a decrease when exercise is taken, probably one reason why exercise is so detrimental to progress in cases of infective hepatitis. Further than this, however, the part played by the mesenteric artery in regulating the flow of blood through the portal vein is not known though McMichael (1932) showed that they were related. The flow of blood through the splenic artery and the part it plays in the production of portal hypertension has been more fully considered, some authors considering that the primary lesion is in the spleen. Pemberton and Kiernan (1945) postulated the presence of a shunt in the spleen so that the blood by-passed the splenic sinuses and reached the splenic vein without the usual reduction in pressure being effected. The part played by shunt mechanisms in the production of lesions in different organs is another subject which has recently been the centre of considerable discussion, especially in relation to the kidney (Trueta et al., 1947). If there is such an entity as primary portal hypertension without either extrahepatic or intrahepatic blockage of the portal or splenic vein, the presence of some such shunt as described by Pemberton and Kiernan would be a reasonable basis on which to explain it. Though both McMichael (1932) and Rousselot (1936) thought that such an entity as primary portal hypertension did exist, to date no authenticated case in the presence of a normal liver and the absence of a block in the portal or splenic vein has been discovered.

Ravenna (1940) considered that in some cases the primary lesion /

lesion was in the small arterioles of the spleen and that the same lesion which caused the periarterial haemorrhages in these cases upset their regulating effect on the flow of blood through the spleen and thus allowed the occurrence of portal hypertension. Here again, before this explanation can be accepted, a properly authenticated case of primary portal hypertension should be produced. Until then it would appear to be more reasonable to accept periarterial haemorrhage as evidence of an already existing increase in portal pressure.

The Causes of Portal Hypertension

Theoretically portal congestion and subsequent portal hypertension may occur when:-

- (1) There is an increased flow of blood into the areas drained by the portal vein without a compensatory increase in the flow of blood out through the hepatic veins.
- (2) There is blockage of the portal vein or narrowing of the lumen in any way, a roughly similar situation to the above being produced for though the diameter of the portal vein is narrowed, there is no corresponding reduction in the amount of blood flowing into it. Blockage of the splenic vein will produce a similar effect in a smaller and more localised segment of the abdominal cavity.
- (3) There is upset of the normal relationship of the hepatic artery to the portal vein.

The possible part played by the spleen in the production of portal hypertension has been discussed and as the present investigation has revealed no case of primary portal hypertension, no further comment on this factor can be made except to point out again that it exists only in theory.

Portal hypertension would therefore appear to be due either to blockage of the portal vein, or the splenic vein (if portal hypertension is taken to include cases with splenomegaly, splenic congestion and the formation of a collateral circulation around the spleen, stomach and oesophagus) or in cases of cirrhosis of the liver to upset of the normal relationship between the portal vein and the hepatic artery. The remainder of this chapter will be occupied by a discussion on the relative importance of these different factors as revealed by a study of the case material and the experimental injection of several cirrhotic livers.

It has been stated already that the blockage in the portal vein may be either intrahepatic or extrahepatic. It is easy to understand the mechanism of production of portal hypertension in a case of extrahepatic obstruction and Case No. 55 is an excellent example of this type of lesion. Here the block was not complete so that there was no obvious damage to the liver or infarction of the bowel and yet there was ample clinical evidence, in the shape of recurrent haematemesis, of the presence of portal hypertension. The partial blockage of the portal vein presumably became more pronounced as the child grew so that the blood circulating through the spleen and the intestines was not able to all pass through the stricture to the liver. /

liver. There was, therefore, congestion of the portal venous bed and as this congestion increased, collateral channels were opened up, congestive splenomegaly developing along with changes in the radicles of the portal vein due to the increase in pressure in them.

The mechanism whereby intrahepatic obstruction is caused is not so easily understood and it was in an endeavour to attain a better understanding of the processes involved in this that the series of injected specimens of cirrhotic livers was prepared. From study of them it was hoped:

- (1) To clarify my own conception of the changes which take place in these livers.
- (2) To see whether, in the cirrhotic liver, there was a freer communication between the portal vein and the hepatic artery than in the normal liver.
- (3) To discover whether there were any marked differences in the vascular pattern produced by diffuse hepatic fibrosis and post-necrotic scarring.

The Injection Experiments

Several authors have used injection techniques to study the vascular supply of the liver and the biliary tracts, notably Mall (1905), McIndoe (1928) and McIndoe and Counsellor (1927). Segall (1923) made a careful study of the vascular pattern of the liver using injections of barium chloride and X-rays. When a quantity of Neoprene Latex became available and it was learned that this substance would penetrate smaller vessels than any previous injection mass, it was thought worth while to repeat McIndoe's /

McIndoe's injection experiments to see if any further light could be thrown on the changes which occur in the blood vessels in cirrhosis of the liver and also to observe to what extent the changes in the vascular pattern depended on the type of cirrhosis present, although, as has already been noted in Part I, it is not always easy to recognise what type of cirrhosis forms the basis of the liver lesion. Comment will however be made on the part this factor plays in the changes in the hepatic vascular pattern.

Livers for injection were obtained from the pathology department of the Royal Infirmary and after several attempts had been made to master the technique of injection, two normal and six cirrhotic livers were injected.

Technique of Injection

It was speedily recognised that one of the main difficulties was to obtain complete injection of the hepatic artery for it was always a comparatively small vessel and unless it was canalised before its bifurcation into its two main branches, considerable difficulty was experienced in tying a cannula into it. Even if the main trunk of the hepatic artery was successfully canalised, injection was not always complete since branches to the liver sometimes originated from other vessels. It was decided, therefore, to remove the liver along with a small piece of the aorta and the coeliac axis and to insert the cannula into the coeliac axis, the other branches of the coeliac axis being tied off after starting the perfusion. This method of injecting the hepatic /

hepatic artery had another advantage for as well as enabling a relatively large cannula which could be tied in firmly to be used, dissection around the porta hepatis was reduced to a minimum. The hepatic artery in the porta hepatis was not easy to define and a considerable amount of dissection was usually necessary before it could be properly exposed. This dissection ruptured many small vascular channels which subsequently gave rise to numerous leaks when perfusion was commenced.

The portal vein was always easily identified and a large cannula could be tied into its main trunk without difficulty.

In only one case (Specimen I) was perfusion of the liver carried out more than 36 hours after death and in this case, as pointed out by Segall (1923), the material was found to be so friable that the numerous leaks were almost impossible to control. Another frequent source of leaks was from small nicks made accidentally in the liver at postmortem. Great care had to be taken therefore in handling the liver and removing it from the body.

The question as to how sections of liver for histological examination could be obtained was one which baulked large and was at first bound up with attempts to seal off leaks present in the liver parenchyma.

Previous workers had found considerable difficulty in cutting sections of tissue the vessels of which had been filled with Neoprime Latex so an attempt was made to evolve a method whereby the section could be taken from the organ before Neoprime was injected, though the removal of a wedge from the edge of the parenchyma reduplicated the problem produced by accidental incision /

incision of the liver. An attempt was made first of all to seal the exposed surfaces with celloidin and cotton wool but as this did not prevent leakage, large artery forceps were placed on either side of the site from which the wedge was to be taken and closed to prevent the Neoprime from penetrating this area. The liver tissue proved too friable for this latter method to be successful and leakage of such large amounts of fluid occurred that it was also abandoned.

Neoprime, when it has become hardened by the action of either formalin or concentrated hydrochloric acid is of rubbery consistence quite different from the consistence of paraffin wax. When, therefore, tissue impregnated with Neoprime is embedded in paraffin wax, the difference in consistence causes marked tearing and torsion of the section without the cutting of the Neoprime. In other words, paraffin wax as a medium does not provide sufficient stability to allow the Neoprime to be sectioned.

It was considered that freezing a formalin fixed section or the embedding of the tissue in celloidin might afford more hope of success and trial sections were taken through using both these methods. It proved possible to obtain sections suitable for pathological examination by both these methods but since technically it was easier to deal with celloidin embedded sections this method was adopted. The main objection to it was the length of time which elapsed before embedding was complete and the sections available for study.

When there were considerable quantities of Neoprime throughout the vessels of the section there was some tearing of the tissues /

tissues but it was possible to cut sections at 10 micron by embedding the blocks in celloidin. The sections were stained with haematoxylin and eosin and examined.

As soon as the liver was removed from the body the coeliac axis and the portal vein were isolated and canalised. The inferior vena cava was slit open to reveal the hepatic veins and the cannula in the hepatic artery connected to a tap. Following the advice of Kelly (1905) the hepatic artery was used for perfusion and a steady flow of water allowed to flow through it. The pressure of flow was not measured but sufficient pressure was used to give good perfusion without too great distension. Once the flow was established as many leaks as possible were identified and the leaking vessels tied off with thread.

Perfusion of the liver through either the portal vein or the hepatic artery but especially through the portal vein, caused an immediate increase in the size of the organ and stoppage of the perfusion almost as rapid deflation. When the perfusion flow was well established, the liver became rounded and tense and very markedly larger than when no fluid was flowing through it. Obviously the collapsed, rather flabby organ, seen at postmortem, does not afford a very good indication of the size and probable palpability of the organ during life, the presence of an active flow of blood through it during life being an obvious explanation for the frequently noted difference in the size of the organ at postmortem and its estimated size during life.

About 30 seconds after commencing perfusion through the hepatic artery a flow of blood-stained fluid was observed to drip from the exposed hepatic veins and a little later a slow drip commenced /

commenced to flow from the canalised portal vein. In some cases, especially in normal livers, the flow from the hepatic artery to the hepatic veins was considerable and the passage from one to the other apparently easy. To wash it through properly, the portal vein was connected up to the tap and the perfusion continued through it for a short time.

The first three or four specimens were perfused overnight but later perfusion was only continued for about three hours and injection performed the same evening. Usually at the end of three hours the return of fluid through the different channels was practically colourless.

Injection of the specimens after perfusion was carried out along the lines suggested by Trueta et al (1947). Pressure was obtained by means of a sphygmomanometer bulb connected to a large Winchester bottle which acted as a reservoir for the compressed air and damped down the too-violent fluctuations in pressure which otherwise occurred when intermittent pumping was required. The Winchester bottle was, in turn, connected to titration flasks containing Neoprine Latex (red for the hepatic artery and blue for the portal vein) and from these rubber tubing led to the canalised vessels. A manometer was incorporated in the apparatus between the Winchester bottle and the titration flasks. Before the different tubes were finally connected up, great care had to be taken to see that no air was present in the injection system, the portal vein and the hepatic artery being filled up with water and the various tubes from the flasks to the vessels filled with Neoprine Latex.

When the various vessels and tubes had been filled with fluid /

fluid, the pressure in the Winchester bottle and in the titration flasks was raised to 200 mm. of mercury, the clip on the tube to the hepatic artery removed and injection of the artery commenced. As the artery was more difficult to inject fully and in the normal liver is of considerably less bulk than the portal vein, it was always injected first, for it was thought that if the large bulk of the portal vein was injected first, many small arterial vessels might be occluded by lateral pressure.

Though Neoprine Latex penetrates small vessels it is important that the injection should be as instantaneous as possible so that the Neoprine does not set in the medium sized vessels and prevent complete injection. For this reason fairly high pressures were used although one successful injection of the portal vein was performed using a pressure of 100 mm. of mercury. The pressure during the injection of the hepatic artery in a normal liver did not usually fall below 150 mm. of mercury but in the cirrhotic liver a few pumps of the sphygmomanometer bulb were usually necessary to prevent the pressure falling below this level. Any leaks which occurred were sealed off as speedily as possible by the application of concentrated hydrochloric acid on the end of a glass rod. This caused the Neoprine to set and so seal off the leak.

When the pressure in the hepatic artery had remained steady for about two minutes, the clip on the tube to the portal vein was opened and the injection material allowed to flow at a pressure of 150 mm. of mercury. In the normal liver successful injection of the portal vein was accompanied by an immediate increase /

increase in the size and consistence of the organ. Usually two flasks of Neoprine were required to complete the injection of the portal vein in the normal liver but only one flask in the cirrhotic liver. The pressure was maintained at about 100 mm. of mercury till the injection of the portal vein was complete and all the leaks were sealed off. The liver was then left a few minutes, the surface carefully cleaned, vessels tied off, pressure released and the tubes disconnected. Usually a slight trickle of blue fluid from the portal veins appeared at the mouths of the hepatic veins but this was usually small in amount.

After a few injections had been successfully performed certain modifications in this technique were introduced. The Neoprine Latex which was coloured red and used for the injection of the hepatic artery was said to contain relatively large particles of colouring matter so that it was possible that injection of this material did not penetrate the capillary tree as far as did the more soluble particles of the blue dyestuff. To investigate and obviate this difference, one cirrhotic liver (Specimen I) was injected using blue Neoprine in the portal vein and white unadulterated Neoprine for the hepatic artery. In this specimen, it was, however, difficult to distinguish the hepatic artery from the portal vein in the fully macerated specimen. In another case, not reported fully since sections from it were not available for study when this commentary was written, the colours were reversed - red being used for the portal vein and blue for the hepatic artery. No gross variation in the degree of penetration of the hepatic artery was noted in this specimen.

It was found to be extremely difficult to orientate the macerated /

macerated specimens properly for apart from the large vessels in the porta hepatis and the gallbladder site, no landmarks remained. In the final two injections therefore, only the outer 2 - 3 cm. of parenchyma was dissolved off and so the shape of the organ retained.

After maceration had proceeded to the required length, the specimen was washed thoroughly and where maceration was complete, immersed in water containing a little phenol, and where some parenchyma remained, the specimen was left in 10 per cent formalin.

Details of the Cases /

Specimen (1) - A normal liver showing slight C.V.D.

In this specimen the right lobe only was injected, a good example of the normal relationship of the portal vein and the hepatic artery being obtained. The injection did not penetrate the fine vessels of the lobules but in some ways this was an advantage when studying these specimens for the full injection was limited to showing the remainder of the vascular tree (Fig. 23).

Specimen (3) - A normal liver

This specimen was injected through the hepatic artery and the portal vein using the usual technique. After two days in concentrated hydrochloric acid, it was washed thoroughly and

DETAILS OF THE CASES

Specimen (A) - A normal liver:

The hepatic and portal veins were injected simultaneously at 200 mm. of mercury. The injection of the hepatic vein appeared all over the surface of the liver, while injection of the portal vein only appeared occasionally on the surface - a further argument in support of the contention that the unit of the liver is the portal vein surrounded by 'central' veins. As was to be expected when two vessels running toward each other were injected, the injection produced a patchy picture, large groups of lobules being injected through one or other vessel. Such an injection would obviously not provide further useful information.

Specimen (B) - A normal liver showing slight C.V.C:

In this specimen the right lobe only was injected, a good example of the normal relationship of the portal vein and the hepatic artery being obtained. The injection did not penetrate the fine vessels of the lobules but in many ways this was an advantage when studying these specimens for too full injection was inclined to obscure the remainder of the vascular tree (Fig. 23).

Specimen (C) - A normal liver:

This specimen was injected through the hepatic artery and the portal vein using the usual technique. After two days in concentrated hydrochloric acid, it was washed thoroughly and fixed /

fixed in 10 per cent formalin. Most of the parenchyma had been dissolved off the left lobe but only the outer 2-3 cm. had been dissolved off the left lobe so that the organ had retained its shape. The injection through the left main branch of the portal vein had penetrated the lobules which were represented by small aggregations of fine capillaries forming small clusters in the ends of the terminal branches of the portal veins (Fig. 22). The right main branch had not been so fully injected so that the medium-sized vessels could be clearly seen, the branches of the portal vein dividing regularly into smaller branches while along with them, often spiralling slightly around them, ran the much smaller branches of the hepatic artery.

In the approximate line of demarcation between the physiological right and left lobes of the liver, a split had developed in the parenchyma and across this split there was no anastomosis between the small branches of the portal vein, but several minute twigs of the hepatic artery did bridge the gap.

Specimen (D) - Case No. 13. 279/48. Male, aet. 48:

The liver was obviously cirrhotic but contained no excess of fibrous tissue. In it though no normal lobules were observed many practically complete lobules were noted. It was considered to show post-necrotic scarring.

There had been repeated haematemesis.

The spleen weighed 240 g..

The injection of this specimen was performed by Mr A.I.S.

McPherson in the Department of Surgery using slightly higher pressures /

pressures than those seen in the other cases in this series. The two main trunks of the portal vein and the right main branch of the hepatic artery were ligatured. There was obvious distortion of the portal vein vascular tree so that it had lost its normal close relationship to the hepatic artery (ligatured in this case with white line).

FIGURE 22

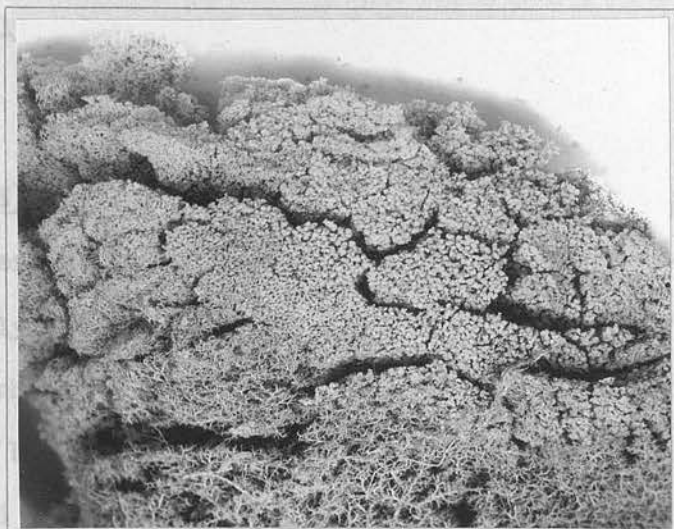


Figure 22 (X1):- Injected cast from specimen 'C' to show the injection of the lobules through the portal vein. In the lower part of the photograph injection is less complete and the medium sized vessels can be seen branching regularly.

From the point of view of the architecture of the liver, there was some upset of the regular architecture in the right lobe and though the upper part of the portal vein divided and branched in a fairly regular manner, the accompanying hepatic artery was larger than usual, almost as large as the portal vein, and instead of terminating when the vein terminated, it often continued on through the substance of the organ for some considerable distance (Fig. 24). In one place an especially prominent branch of the hepatic artery travelled for 4 - 5 cm. across the surface of the specimen.

pressures than those used in the other cases in this series.

The two main trunks of the portal vein and the right main branch of the hepatic artery were injected. There was obvious distortion of the portal vein vascular tree so that it had lost its normal close relationship to the hepatic artery (injected in this case with white Neoprine). The branches of the hepatic artery running over the surface and through the right lobe were conspicuously enlarged and elongated.

Specimen (E) - Case No. 23. 600/48. Male, aet. 60:

The left lobe of the liver was almost completely atrophic and a widely patent umbilical vein arose from the left main branch of the portal vein. There were no oesophageal varices presumably because of the efficient collateral circulation established elsewhere.

The spleen weighed 420 g..

One of the main features of this specimen was the numerous elongated and tortuous anastomotic channels which had developed from the portal vein in the region of the left lobe. There was some upset of the vascular architecture in the right lobe and though the units of the portal vein divided and branched in a fairly regular pattern, the accompanying hepatic artery was larger than usual, almost as large as the portal vein, and instead of terminating when the vein terminated, it often continued on through the substance of the organ for some considerable distance (Fig. 24). In one place an especially prominent branch of the hepatic artery travelled for 4 - 5 cm. across the surface of the specimen.

Specimen (F) - Case No. 24. 614/48. Male, aet. 44 /

FIGURE 23

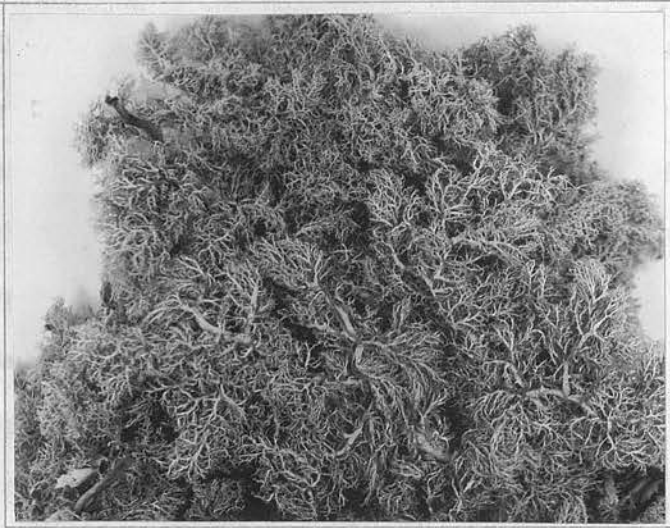


Figure 23 (X1): Injected cast from specimen 'B' to show the regular branching of the portal vein (pale) and hepatic artery (dark) and their relation to each other.

FIGURE 24



Figure 24 (X1): Injected cast from specimen 'E' to show the vascular pattern in a cirrhotic liver. Though the vessels still branch fairly regularly and retain their relationship to each other, the hepatic artery (dark) is more prominent than usual and in the small segment near the centre of the field, the artery (dark) can be seen continuing beyond the territory of the accompanying portal vein (pale).

Specimen (F) - Case No. 24. 614/48. Male, aet. 44:

The liver was diffusely nodular and showed the microscopic appearance of well marked 'portal' cirrhosis with no clue as to the type of cirrhosis from which it originated though on the basis of the naked-eye appearance it was classified as a case of diffuse hepatic fibrosis.

The patient had had several haematemeses.

The spleen weighed 450 g..

Injection of the hepatic artery was particularly successful, the injection being so complete that this was the only specimen where the shape of the liver was retained after maceration.

One small segment of the hepatic artery in the right lobe had escaped injection and in this area the portal vein was seen to present a very stunted and irregular appearance. As the technique of injection was not varied in (Fig.25) this case and the injection of so many small tributaries of the hepatic artery was not seen in any of the other specimens, the extraordinary length and fineness of the ramifications of the hepatic artery were regarded as true features of this case.

Specimen (G) - Case No. 25. 615/48. Male, aet. 40:

The liver was small and nodular with a large area of completely fibrotic liver tissue between the right and left lobes. The microscopic appearance gave no clue as to the type of cirrhosis present but in view of the naked-eye appearance, this was labelled a case of post-necrotic scarring.

There had been no haematemesis.

The spleen weighed 450 g..

The /

FIGURE 25



Figure 25 (X1): Injected cast from specimen 'F' to show the fine injection of the hepatic artery in the right lobe in contrast to the stunted portal vein tree of the left lobe where the hepatic artery was not injected.

Specimen (3) - 3/24/55 - 34/55 - Female, age 62

The liver was small, shrunken and regularly nodular. There was a history of chronic alcoholism and though in view of the type of cirrhosis was obtained from microscopic examination, in view of the macroscopic appearance and the history, this was considered to be a case of diffuse hepatic fibrosis.

There had been no neoplasia.

The spleen weighed 50 g.

The

The main trunk of the hepatic artery had been severed high up and the left branch of the hepatic artery proved to be too small for injection. Otherwise, the injection was carried out as usual. On washing the specimen after macerating it for two days, numerous small nodules, varying from 0.2 - 1.0 cm. in diameter, were floated out from among the network of injected vessels. The injection had apparently not entered these nodules at all for they lay quite loosely and as far as could be made out, unattached. It was considered that they represented hyperplastic nodules of liver tissue and section of them revealed very autolytic but faintly recognisable islands of liver cells with little fibrous tissue through them.

The main feature of the washed specimen was the marked predominance of the hepatic artery as compared with the portal vein. The whole specimen was small and the portal vein tree markedly irregular. The main bulk of the injection mass consisted of dilated and elongated hepatic arteries which, on the under surface of the left lobe, were almost as finely injected as in specimen 'F' (Fig. 26).

Specimen (H) - Case No. 26. 54/49. Female, aet. 64:

The liver was small, shrunken and regularly nodular. There was a history of marked alcoholism and though no clue as to the type of cirrhosis was obtained from microscopic examination, in view of the naked-eye appearance and the history, this was considered to be a case of diffuse hepatic fibrosis.

There had been no haematemesis.

The spleen weighed 500 g..

The /

FIGURE 26



Figure 26 (X1): Injected cast from specimen 'G' to show the complete loss of normal vascular architecture in an advanced case of cirrhosis of the liver. The hepatic artery (dark or white) is now the predominant vessel, the portal vein (grey) being much reduced in volume.

The injection of the right main branch of the hepatic artery (in white) was incomplete perhaps because one of the main branches may have been tied off when the many very friable bleeding points around the hilum were secured. That autolysis was very marked was confirmed on examination of the specimen for many small ruptures were visible in the smallest vessels. The artery was slightly more prominent than in a normal specimen and it also appeared to anastomose more freely with neighbouring vessels though with these fine ramifications it was often difficult to decide whether the slender thread-like vessel was white or pale blue in colour. Though no gross distortion of the vascular tree was present, the whole vascular tree had lost some of its normal regularity of arrangement.

Specimen (I) - Case No. 28. 79/49. Female, aet. 39:

The patient died of gross mitral stenosis and recurring heart failure. The left lobe of the liver was grossly reduced in size and the right lobe, as well as being slightly reduced in size, was coarsely nodular. A normal lobule was noted on microscopic examination so though it was thought that the whole picture might be accounted for by the presence of a cardiac cirrhosis, it was put down as one of post-necrotic scarring.

There had been no haematemesis.

The spleen weighed 380 g..

The flow of perfusion fluid through the portal vein was markedly diminished when all the anastomotic channels over the surface of the liver had been tied off. Maceration was allowed to continue /

continue for three days, the specimen was thoroughly washed and the whole placed in 10 per cent formalin to harden. On examination, the branches of both the hepatic artery and the portal vein were observed to run in the strands of fibrous tissue surrounding the nodules of liver tissue and as in specimen 'E', so far as could be made out, no vessels penetrated these nodules. Judging from the small strands of vessels available for inspection, the total vascular bed was markedly diminished though the hepatic artery and portal vein retained their normal relationship to each other to a degree altogether surprising, in view of the marked cirrhosis.

DISCUSSION /

DISCUSSION

On the Findings in the Injection Experiments

Probably the most striking feature that study of these specimens demonstrates is the difference in the vascular patterns of all six cirrhotic livers studied. After reading the description given by McIndoe (1928) of the disruption of the normal relationship between the portal vein and the hepatic artery which occurs in cases of cirrhosis, it was rather surprising to find so little dissociation of the two sets of vessels in specimens (H) and (I) and to a less extent, in specimen (E). The distortion of the vascular pattern was most marked in specimen (G) and was also a marked feature of specimen (D). In specimen (F) the disruption was again well-marked but was overshadowed by the extraordinarily dense network of small arterial vessels present throughout. Both specimens (G) and (D) had been diagnosed when studied in Part I as cases of post-necrotic scarring, while specimen (H) was diagnosed as a case of diffuse hepatic fibrosis. It would appear, therefore, that the distortion of the vascular pattern is most marked in cases of post-necrotic scarring - a finding in line with the more marked distortion of the parenchyma which occurs in these cases.

It has been noted already that injection of the normal liver reveals the portal vein as the larger vessel, the branches of the hepatic artery being much smaller than those of the portal vein which they accompany. In the markedly cirrhotic liver this relationship becomes reversed and study of specimen (E) would appear to provide a possible reason as to how this could come about.

In /

In the normal liver small branches of the hepatic artery were noted to anastomose with one another. This anastomosis is accentuated in the injected specimen of the right lobe in specimen (E), the branches of the hepatic artery being slightly enlarged and more nearly approximating to the size of the portal vein than in the normal liver while, though the relationship of the hepatic artery to the portal vein was on the whole, well maintained, in one or two places the slightly hypertrophied hepatic artery was noted to extend beyond the corresponding branch of the portal vein to anastomose with another branch of the hepatic artery. It is suggested that this arrangement is an exaggeration of the normal anastomosis present between the small branches of the hepatic artery. By the opening up of these channels, increase in the size of the hepatic artery and some decrease in the size and probably some obliteration of the branches of the portal vein, the picture seen in advanced cases of cirrhosis is produced (Figs. 23, 24, 25 and 26).

As Kretz (1905) and McIndoe (1928) noted, the nodules of hypertrophic liver cells appear to be supplied through the hepatic artery and not the portal vein - a finding borne out in the injected material studied. There is therefore, in all these cases, some diminution in the portal vein bed probably not completely compensated for by dilatation of the remaining portal vessels. That the number of branches and the amount of the injection required to fill the portal vein are diminished in some cases was obvious, but the diminution in the total portal vein vascular bed is not an entity susceptible of further proof except perhaps by carefully controlled weighing of the injected portal /

portal vascular tree. It was however noted that, while a normal liver required two flaskfuls of Neoprime Latex, a cirrhotic liver usually required only one. This is not, however, a very accurate indication of the amount of Neoprime required for this depended largely on the number of leaks present in the specimen during injection.

The marked increase in the size and number of the branches of the hepatic artery was a more definite feature of some of these specimens, the main reason for the increase being presumably, to maintain a blood supply to the nodules of hypertrophied liver tissue, the attempt being exceptionally successful in specimen (F). In this same specimen the stunted and irregular appearance of the portal vein in the uninjected segment appeared to support McIndoe's (1928) point that little or no blood reached the liver cells from the portal vein in these cases but that the blood merely runs from the portal vein through smaller vessels to anastomotic channels. This point is further substantiated by the finding in specimen (I)' where the inflow through the portal vein was so markedly reduced when all the anastomotic channels were tied off.

It was hoped that study of these specimens under a dissecting microscope would show whether there was an anastomosis present in the cirrhotic livers between the portal vein and the hepatic artery. However, study of the distorted vascular patterns in the cirrhotic liver proved more difficult than was anticipated and even in the normal liver the picture under the dissecting microscope was so confused and difficult to interpret that little help in the understanding of the various patterns was obtained in /

in this way. So far as could be made out, there was no abnormal anastomosis between the hepatic artery and the portal vein in the specimens of cirrhotic livers examined, but in view of the difficulty experienced in examining the specimens, it is not easy to know how much stress to lay on this finding and it is doubtful whether theories of portal hypertension based on theoretical considerations of the too-speedy meeting of the hepatic artery and the portal vein streams could be altogether ruled out by the absence of such anastomoses in the specimens.

Case No. 35 is of considerable interest in respect of this theoretical relationship of the hepatic artery and portal vein for here was a possible case of cirrhosis with co-existing hypertension. If the distortion of the lobular architecture is a true finding in this case and the presence in the hepatic artery does play a part in the production of portal hypertension, one would expect the portal hypertension to be marked in this case. It is difficult to judge whether or not this was the case except that the spleen (600 g.) was considerably larger than is usual in a case of pure cardiac congestion (McMichael, 1934). If the congestion in this case was "active" (Hueck, 1928 - 29) the theory that the portal hypertension was due to early cirrhosis in the presence of systemic hypertension provides an explanation for the enlargement of the spleen - a finding otherwise very difficult to explain.

From examination of the cases studied in Part I and in the injection experiments it is obvious that one of the fundamental disturbances in cases of cirrhosis of the liver is the upset in lobular architecture. This upset is brought about by the /

the death of some liver cells and regeneration of others so that the normal delicate relationship of the liver cells to the various vascular and bile channels is disturbed. The cases labelled cardiac cirrhosis demonstrate the earliest changes which occur in cirrhosis of the liver, a feature of some of these cases being the amount of cellular activity present (Fig. 3).

As each liver cell has a bile channel on one side and a sinusoid on the other, it would appear that the pathological degree of cellular activity shown in some of these cases could readily cause upset of this arrangement for a cell with many nuclei will, presumably, eventually give rise to a similar number of liver cells which, if of a large enough number, will not retain this delicate relationship of cells to vessels. Discussing this point Ashworth and Reid (1947) stated that the lobular architecture is maintained unless the damage to the liver cells and subsequent regeneration of cells is very severe, when cirrhosis may result.

Another feature of early cirrhosis of the liver, seen best in the biopsy specimens, is the gradual pushing aside of the central veins and their eventual incorporation in the portal tracts. The death of liver cells and the regeneration of other liver cells must therefore be a process affecting different parts of the lobules in different ways. It is suggested that one of the factors in determining this is the blood supply of that portion and whether it derives from the hepatic artery or the portal vein.

Mann and Magath (1922) and later Cameron and de Saren (1939) considered that portal venous blood is essential for the growth and /

and regeneration of hepatic cells and Olds and Stafford (1930) showed that peripheral sinusoids were supplied by branches of the portal vein or the hepatic artery, but never by both. It is possible, therefore, that the regenerative powers of cells supplied by the portal vein tributaries are superior to those of cells supplied by the hepatic artery and this may be a further factor leading to possible distortion of the lobule.

McIndoe (1928) considered that in cirrhosis of the liver there was gradual sclerosis of the portal vein so that if the portal blood flow is so important to the regeneration processes in the liver it is possible that whether the cirrhosis is due to post-necrotic scarring or diffuse hepatic fibrosis, there is sclerosis of the portal vein producing secondary changes in the liver. In the end it may, therefore, be impossible to decide the type of cirrhosis from which the lesion originated. This theory derives support from the findings set out in Part I and provides an explanation as to why so many cases of cirrhosis had to be labelled indeterminate in type.

While studying the case material it was noted that in the cirrhotic liver multinucleated liver cells were most frequently visible around the periphery of the nodules of liver cells and study of the injection specimens showed that these nodules received little blood from the portal vein. These two findings together give added support to the hypothesis that portal blood enables regeneration of liver cells to occur for in these cases it is apparently only the peripheral cells which receive portal blood and maintain the function of the liver.

CONCLUSIONS

While study of the case material and the injection specimens has provided material for the discussion of several different aspects of portal hypertension, many of the premises on which these points are based - for instance, that portal blood is essential for the regeneration of liver cells - are, themselves, insecurely based on fact. A few well-defined points have, however, been made:

- (1) The vascular pattern in cirrhosis showed varying degrees of distortion in the specimens injected. The ways in which this distortion is brought about have been discussed and some of the conclusions arrived at have derived support from the case material examined.
- (2) One of the main features of the injection specimens is the remarkable variation in the vascular pattern of the cirrhotic livers, no two specimens showing the same features. The disruption of the vascular pattern is more marked in cases of post-necrotic scarring than in cases of diffuse hepatic fibrosis.
- (3) In the cirrhotic liver there is a gradual decrease in the size of the portal vascular bed and a corresponding increase in the vascular bed of the hepatic artery. The methods by which this is brought about we discussed, and one method by which it occurs is described.
- (4) In two of the injection specimens, the hypertrophied nodules /

modules of liver cells received no blood vessels at all, while in one, the completeness of the injection of the hepatic artery suggested the modules were supplied by it.

- (5) Portal hypertension will occur when there is diminution or narrowing of the portal vascular bed. It has been demonstrated that the number of branches of the portal vein but not that the total portal vein bed is reduced, though it is suggested that this is probably the case. Till a decrease in the portal vascular bed is demonstrated not to occur in cirrhosis of the liver, this must remain the most probable cause of portal hypertension.

- (6) In one case it appears probable, on theoretical grounds, that the increased pressure in the hepatic artery and distortion of the normal relationship of the portal vein to the hepatic artery, played a part in the production of portal hypertension but that this relationship of the two vessels to each other is of importance in this connection, derives no positive proof from study of the injected specimens.

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